respect to a particular polymorphic form of a compound means that the composition comprising the polymorphic form contains less than 95%, less than 90%, less than 80%, less than 70%, less than 65%, less than 60%, less than 55%, less than 50%, less than 40%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, or less than 1% by weight of other substances, including other polymorphic forms and/or impurities. In certain embodiments, "substantially pure" or "substantially free of" refers to a substance free of other substances, including other polymorphic forms and/or impurities. Impurities may, for example, include by-products or left over reagents from chemical reactions, contaminants, degradation products, other polymorphic forms, water, and solvents.

Formula III

[0180] Provided are also compositions comprising at least one, or all of polymorphs (*e.g.*, any one or more of Formula III polymorphic Forms I, II, and III) as described herein. In a particular embodiment, a composition comprising one of Formula III polymorphic Forms I, II, and III described herein is provided. In a particular embodiment, a composition comprising two of Formula IIII polymorphic Forms I, II, and III described herein is provided. In other embodiments, the compositions described herein may comprise substantially pure polymorphic forms, or may be substantially free of other polymorphs and/or impurities.

[0181] In some embodiments, the composition comprises a polymorphic form of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments are provided compositions comprising a polymorphic form as described herein, wherein the potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate within the composition is substantially pure (*i.e.*, substantially pure Form I, II, and/or III). In particular embodiments of compositions comprising a polymorphic form of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-

methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate present in the composition is one of the polymorphic forms disclosed herein. In certain embodiments, the composition includes at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% of one of the polymorphic forms potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0182] In other embodiments of compositions comprising a polymorphic form disclosed herein, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1% of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate present in the composition are other polymorphs of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate and/or impurities.

[0183] In yet other embodiments of compositions comprising the polymorphic forms disclosed herein, impurities make up less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1% of the total mass relative to the mass of the polymorphic forms present. Impurities may, for example, include by-products from synthesizing potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, contaminants, degradation products, other polymorphic forms, water, and solvents. In certain embodiments, impurities include by-products from the process of synthesizing potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments, impurities include contaminants from the process of synthesizing potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments, impurities include degradation products of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments,

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impurities include other polymorphic forms of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments, impurities include water or solvent. In certain embodiments of compositions comprising a polymorphic form disclosed herein, impurities are selected from the group consisting of by-products from synthesizing potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, contaminants, degradation products, other polymorphic forms, water, solvents and combinations thereof.

[0184] In yet other embodiments, the composition comprising a polymorphic form disclosed herein has less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about 1% by weight of amorphous or non-crystalline potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0185] Provided are also compositions comprising at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, or all of polymorphs (e.g., any one or more of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII, Formula II polymorphic Form I, and/or Formula III polymorphic Forms I, II, and III) as described herein. In a particular embodiment, a composition comprising one of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII, Formula II polymorphic Form I, and/or Formula III polymorphic Forms I, II, and III described herein is provided. In a particular embodiment, a composition comprising two of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII, Formula II polymorphic Form I, and/or Formula III polymorphic Forms I, II, and III described herein is provided. In a particular embodiment, a composition comprising three of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII, Formula II polymorphic Form I, and/or Formula III polymorphic Forms I, II, and III described herein is provided. In a particular embodiment, a composition comprising four of Formul Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII, Formula II polymorphic Form I, and/or Formula III polymorphic Forms I, II, and III described herein is provided. In a particular embodiment, a composition comprising five of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII, Formula II polymorphic Form I, and/or Formula III polymorphic Forms I, II, and III described herein is provided. In a particular embodiment, a composition

comprising six of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII, Formula II polymorphic Form I, and/or Formula III polymorphic Forms I, II, and III described herein is provided. In a particular embodiment, a composition comprising seven of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII, Formula II polymorphic Form I, and/or Formula III polymorphic Forms I, II, and III described herein is provided. In a particular embodiment, a composition comprising eight of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII, Formula II polymorphic Form I, and/or Formula III polymorphic Forms I, II, and III described herein is provided. In a particular embodiment, a composition comprising nine of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII, Formula II polymorphic Form I, and/or Formula III polymorphic Forms I, II, and III described herein is provided. In a particular embodiment, a composition comprising ten of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII, Formula II polymorphic Form I, and/or Formula III polymorphic Forms I, II, and III described herein is provided. In a particular embodiment, a composition comprising eleven of Formula I polymorphic Forms I, II, III, IV, V, VI, VII, and VIII, Formula II polymorphic Form I, and/or Formula III polymorphic Forms I, II, and III described herein is provided. In other embodiments, the compositions described herein may comprise substantially pure polymorphic forms, or may be substantially free of other polymorphs and/or impurities.

[0186] In some embodiments, the term "substantially pure" or "substantially free" with respect to a particular polymorphic form of a compound means that the composition comprising the polymorphic form contains less than 95%, less than 90%, less than 80%, less than 70%, less than 65%, less than 60%, less than 55%, less than 50%, less than 40%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, or less than 1% by weight of other substances, including other polymorphic forms and/or impurities. In certain embodiments, "substantially pure" or "substantially free of" refers to a substance free of other substances, including other polymorphic forms and/or impurities. Impurities may, for example, include by-products or left over reagents from chemical reactions, contaminants, degradation products, other polymorphic forms, water, and solvents.

[0187] Administration of the compounds of the invention in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration of agents for serving similar utilities. The pharmaceutical compositions of the invention can be prepared by combining a compound of the invention with an appropriate

pharmaceutically acceptable carrier, diluent or excipient, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. The pharmaceutical compositions of the invention can be prepared by combining a compound of the invention with an appropriate pharmaceutically acceptable carrier, diluent or excipient, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as solid dispersions and solid solutions. Typical routes of administering such pharmaceutical compositions include, without limitation, oral, topical, transdermal, inhalation, parenteral, sublingual, buccal, rectal, vaginal, and intranasal. In one embodiment, the pharmaceutical compositions is prepared for oral administration. In a specific embodiment, the pharmaceutical composition is a tablet. Pharmaceutical compositions of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient. Compositions that will be administered to a subject or patient take the form of one or more dosage units, where for example, a tablet may be a single dosage unit, and a container of a compound of the invention in aerosol form may hold a plurality of dosage units. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*, 20th Edition (Philadelphia College of Pharmacy and Science, 2000). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention for treatment of a disease or condition of interest in accordance with the teachings of this invention.

[0188] The pharmaceutical compositions of the invention may be prepared by methodology well known in the pharmaceutical art. For example, a pharmaceutical composition intended to be administered by injection can be prepared by combining a compound of the invention with sterile, distilled water so as to form a solution. A surfactant may be added to facilitate the formation of a homogeneous solution or suspension. Surfactants are compounds that non-covalently interact with the compound of the invention so as to facilitate dissolution or homogeneous suspension of the compound in the aqueous delivery system.

[0189] For example, a solid pharmaceutical composition intended for oral administration can be prepared by mixing a compound of the invention with at least one suitable pharmaceutical excipient to form a solid preformulation composition, which then may be

readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. Accordingly, in one embodiment, a pharmaceutical composition is provided, which includes a compound of Formula (I), (II), or (III) and a pharmaceutical excipient.

[0190] The compounds of the invention are administered in a therapeutically effective amount, which will vary depending upon a variety of factors including the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disorder or condition; and the subject undergoing therapy. In some embodiments, the compounds of the invention can be administered alone or in combination with other antiviral agents once or twice daily for as long as the patient is infected, latently infected, or to prevent infection (e.g. for multiple years, months, weeks, or days).

Combination Therapy

[0191] In one embodiment, a method for treating or preventing an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein in combination with a therapeutically effective amount of one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents. In one embodiment, a method for treating an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein in combination with a therapeutically effective amount of one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents.

[0192] In one embodiment, a method for treating an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound or composition disclosed herein in combination with a therapeutically effective amount of one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents.

[0193] In certain embodiments, the present invention provides a method for treating an HIV infection, comprising administering to a patient in need thereof a therapeutically effective amount of a compound or composition disclosed herein in combination with a

therapeutically effective amount of one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0194] One embodiment provides a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents for use in a method for treating or preventing an HIV infection in a human having or at risk of having the infection. One embodiment provides a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents for use in a method for treating an HIV infection in a human having or at risk of having the infection. One embodiment provides a compound disclosed herein for use in a method for treating or preventing an HIV infection in a human having or at risk of having the infection, wherein the compound is administered in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents. One embodiment provides a compound disclosed herein for use in a method for treating an HIV infection in a human having or at risk of having the infection, wherein the compound is administered in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents. In certain embodiments, the present invention provides a compound disclosed herein in combination with one or more additional therapeutic agents which are suitable for treating an HIV infection, for use in a method for treating an HIV infection. In certain embodiments, the present invention provides a compound disclosed herein for use in a method for treating an HIV infection, wherein the compound is administered in combination with one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0195] One embodiment provides the use of a compound disclosed herein thereof, in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents in the manufacture of a medicament for treating or preventing an HIV infection in a human having or at risk of having the infection. One embodiment provides the use of a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents in the manufacture of a medicament for treating an HIV infection in a human having or at risk of having the infection. One embodiment provides the use of a compound disclosed herein in the manufacture of a medicament for treating or preventing an HIV infection in a human having or at risk of having the infection, wherein the compound is administered in combination with one or more

(e.g., one, two, three, one or two, or one to three) additional therapeutic agents. One embodiment provides the use of a compound disclosed herein thereof, in the manufacture of a medicament for treating an HIV infection in a human having or at risk of having the infection, wherein the compound is administered in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents. In certain embodiments, the present invention provides the use of a compound disclosed herein thereof, in combination with one or more additional therapeutic agents which are suitable for treating an HIV infection, in treating an HIV infection. In certain embodiments, the present invention provides the use of a compound disclosed herein thereof for treating an HIV infection, wherein the compound is administered in combination with one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0196] A compound as disclosed herein (e.g., any compound of Formulas (I), (II), and/or (III)) may be combined with one or more additional therapeutic agents in any dosage amount of the compound of Formulas (I), (II), and/or (III) (e.g., from 50 mg to 1000 mg of compound).

[0197] In one embodiment, pharmaceutical compositions comprising a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent or excipient are provided.

[0198] In one embodiment, combination pharmaceutical agents comprising a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents are provided.

[0199] In one embodiment, kits comprising a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents are provided.

[0200] In the above embodiments, the additional therapeutic agent may be an anti-HIV agent. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, entry inhibitors (e.g., CCR5 inhibitors, gp41 inhibitors (i.e., fusion inhibitors) and CD4 attachment inhibitors),

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CXCR4 inhibitors, gp120 inhibitors, G6PD and NADH-oxidase inhibitors, compounds that target the HIV capsid ("capsid inhibitors"; e.g., capsid polymerization inhibitors or capsid disrupting compounds such as those disclosed in WO 2013/006738 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), and WO 2013/006792 (Pharma Resources), pharmacokinetic enhancers, and other drugs for treating HIV, and combinations thereof.

[0201] In other embodiments, the additional therapeutic agent may be an anti-HIV agent. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors (e.g., CCR5 inhibitors, gp41 inhibitors (i.e., fusion inhibitors) and CD4 attachment inhibitors), CXCR4 inhibitors, gp120 inhibitors, G6PD and NADH-oxidase inhibitors, HIV vaccines, HIV maturation inhibitors, latency reversing agents (e.g., histone deacetylase inhibitors, proteasome inhibitors, protein kinase C (PKC) activators, and BRD4 inhibitors), compounds that target the HIV capsid ("capsid inhibitors"; e.g., capsid polymerization inhibitors or capsid disrupting compounds, HIV nucleocapsid p7 (NCp7) inhibitors, HIV p24 capsid protein inhibitors), pharmacokinetic enhancers, immune-based therapies (e.g., Pd-1 modulators, Pd-L1 modulators, toll like receptors modulators,, IL-15 agonists,), HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins (e.g., DARTs®, Duobodies®, Bites®, XmAbs®, TandAbs ®, Fab derivatives) including those targeting HIV gp120 or gp41, combination drugs for HIV, HIV p17 matrix protein inhibitors, IL-13 antagonists, Peptidyl-prolyl cis-trans isomerase A modulators, Protein disulfide isomerase inhibitors, Complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, Integrin antagonists, Nucleoprotein inhibitors, Splicing factor modulators, COMM domain containing protein 1 modulators, HIV Ribonuclease H inhibitors, Retrocyclin modulators, CDK-9 inhibitors, Dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, Ubiquitin ligase inhibitors, Deoxycytidine kinase inhibitors, Cyclin dependent kinase inhibitors Proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, HIV gene therapy, PI3K inhibitors, compounds such as those

disclosed in WO 2013/006738 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), WO 2013/091096A1 (Boehringer Ingelheim), WO 2009/062285 (Boehringer Ingelheim), US20140221380 (Japan Tobacco), US20140221378 (Japan Tobacco), WO 2010/130034 (Boehringer Ingelheim), WO 2013/159064 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO2012/003497 (Gilead Sciences), WO2014/100323 (Gilead Sciences), WO2012/145728 (Gilead Sciences), WO2013/159064 (Gilead Sciences) and WO 2012/003498 (Gilead Sciences) and WO 2013/006792 (Pharma Resources), and other drugs for treating HIV, and combinations thereof.

[0202] In certain embodiments, the additional therapeutic is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof.

[0203] In certain embodiments a compound of Formulas (I), (II), and/or (III) is formulated as a tablet, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the tablet can contain another active ingredient for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof. In certain embodiments, the tablet can contain one or more active ingredients for treating HIV, such as HIV nucleoside or nucleotide inhibitors of reverse transcriptase. In certain embodiments, such tablets are suitable for once daily dosing.

[0204] In further embodiments, the additional therapeutic agent is selected from one or more of:

(1) HIV protease inhibitors selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;

(2) HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase selected from the group consisting of capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, TMC-120, rilpivirine, BILR 355 BS, VRX 840773, lersivirine (UK-453061), RDEA806, KM023 and MK-1439;

(3) HIV nucleoside or nucleotide inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, abacavir sulfate, amdoxovir, elvucitabine, alovudine, MIV-210, ±-FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), KP-1461, GS-9131 (Gilead Sciences), fosalvudine tidoxil (formerly HDP 99.0003), tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir alafenamide hemifumarate, tenofovir alafenamide fumarate (Gilead Sciences), GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxil, CMX-001 (Chimerix) and CMX-157 (Chimerix);

(4) HIV integrase inhibitors selected from the group consisting of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, AR-177, L-870812, and L-870810, raltegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, BA 011, elvitegravir, dolutegravir, dolutegravir sodium, and GSK-744;

(6) HIV non-catalytic site, or allosteric, integrase inhibitors (NCINI) including, but not limited to, BI-224436, CX0516, CX05045, CX14442, compounds disclosed in WO 2009/062285 (Boehringer Ingelheim), WO 2010/130034 (Boehringer Ingelheim), WO 2013/159064 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO 2012/003497 (Gilead Sciences), WO 2012/003498 (Gilead Sciences) each of which is incorporated by references in its entirety herein;

(7) gp41 inhibitors selected from the group consisting of enfuvirtide, sifuvirtide, albuvirtide, FB006M, and TRI-1144;

(8) the CXCR4 inhibitor AMD-070;

(9) the entry inhibitor SP01A;

(10) the gp120 inhibitor BMS-488043;

(11) the G6PD and NADH-oxidase inhibitor immunitin;

(12) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

(13) CD4 attachment inhibitors selected from the group consisting of ibalizumab (TMB-355) and BMS-068 (BMS-663068);

(14) pharmacokinetic enhancers selected from the group consisting of cobicistat and SPI-452; and

(15) other drugs for treating HIV selected from the group consisting of BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), HRG214, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040),

and combinations thereof.

[0205] In certain embodiments, the additional therapeutic agent is selected from one or more of:

(1) Combination drugs selected from the group consisting of ATRIPLA® (efavirenz+tenofovir disoproxil fumarate +emtricitabine), COMPLERA® or EVIPLERA® (rilpivirine+tenofovir disoproxil fumarate +emtricitabine), STRIBILD® (elvitegravir+cobicistat+tenofovir disoproxil fumarate +emtricitabine), dolutegravir + abacavir sulfate +lamivudine, TRIUMEQ® (dolutegravir + abacavir + lamivudine), lamivudine + nevirapine + zidovudine, dolutegravir+rilpivirine, dolutegravir+rilpivirine hydrochloride, atazanavir sulfate + cobicistat, atazanavir + cobicistat, darunavir + cobicistat, efavirenz + lamivudine + tenofovir disoproxil fumarate, tenofovir alafenamide hemifumarate + emtricitabine + cobicistat + elvitegravir, tenofovir alafenamide hemifumarate + emtricitabine, tenofovir alafenamide + emtricitabine, tenofovir alafenamide hemifumarate + emtricitabine + rilpivirine, tenofovir alafenamide + emtricitabine + rilpivirine , Vacc-4x + romidepsin, darunavir + tenofovir alafenamide hemifumarate+ emtricitabine + cobicistat, APH-0812, raltegravir + lamivudine, KALETRA® (ALUVIA®, lopinavir+ritonavir), atazanavir sulfate + ritonavir, COMBIVIR® (zidovudine+lamivudine, AZT+3TC),

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EPZICOM® (Kivexa®, abacavir sulfate +lamivudine, ABC+3TC), TRIZIVIR® (abacavir sulfate+zidovudine+lamivudine, ABC+AZT+3TC), TRUVADA® (tenofovir disoproxil fumarate +emtricitabine, TDF+FTC), doravirine + lamivudine + tenofovir disoproxil fumarate, doravirine + lamivudine + tenofovir disoproxil, tenofovir + lamivudine and lamivudine + tenofovir disoproxil fumarate;

(2) HIV protease inhibitors selected from the group consisting of amprenavir, atazanavir, fosamprenavir, fosamprenavir calcium, indinavir, indinavir sulfate, lopinavir, ritonavir, nelfinavir, nelfinavir mesylate, saquinavir, saquinavir mesylate, tipranavir, brecanavir, darunavir, DG-17, TMB-657 (PPL-100) and TMC-310911;

(3) HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase selected from the group consisting of delavirdine, delavirdine mesylate, nevirapine, etravirine, dapivirine, doravirine, rilpivirine, efavirenz, KM-023, VM-1500, lentinan and AIC-292;

(4) HIV nucleoside or nucleotide inhibitors of reverse transcriptase selected from the group consisting of VIDEX® and VIDEX® EC (didanosine, ddI), zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, censavudine, abacavir, abacavir sulfate, amdoxovir, elvucitabine, alovudine, phosphazid, fozivudine tidoxil, apricitabine, amdoxovir , KP-1461, fosalvudine tidoxil, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, tenofovir alafenamide hemifumarate, tenofovir alafenamide fumarate, adefovir, adefovir dipivoxil, and festinavir;

(5) HIV integrase inhibitors selected from the group consisting of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, raltegravir, elvitegravir, dolutegravir and cabotegravir;

(6) HIV non-catalytic site, or allosteric, integrase inhibitors (NCINI) selected from the group consisting of CX-05168, CX-05045 and CX-14442;

(7) HIV gp41 inhibitors selected from the group consisting of enfuvirtide, sifuvirtide and albuvirtide;

(8) HIV entry inhibitors selected from the group consisting of cenicriviroc;

(9) HIV gp120 inhibitors selected from the group consisting of Radha-108 (Receptol) and BMS-663068;

(10) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, Adaptavir (RAP-101), nifeviroc (TD-0232), TD-0680, and vMIP (Haimipu);

(11) CD4 attachment inhibitors selected from the group consisting of ibalizumab;

(12) CXCR4 inhibitors selected from the group consisting of plerixafor, ALT-1188, vMIP and Haimipu;

(13) Pharmacokinetic enhancers selected from the group consisting of cobicistat and ritonavir;

(14) Immune-based therapies selected from the group consisting of dermaVir, interleukin-7, plaquenil (hydroxychloroquine), proleukin (aldesleukin, IL-2), interferon alfa, interferon alfa-2b, interferon alfa-n3, pegylated interferon alfa, interferon gamma, hydroxyurea, mycophenolate mofetil (MPA) and its ester derivative mycophenolate mofetil (MMF), WF-10, ribavirin, IL-2, IL-12, polymer polyethyleneimine (PEI), Gepon, VGV-1, MOR-22, BMS-936559, toll-like receptors modulators (tlr1, tlr2, tlr3, tlr4, tlr5, tlr6, tlr7, tlr8, tlr9, tlr10, tlr11, tlr12 and tlr13), rintatolimod and IR-103;

(15) HIV vaccines selected from the group consisting of peptide vaccines, recombinant subunit protein vaccines, live vector vaccines, DNA vaccines, virus-like particle vaccines (pseudovirion vaccine), CD4-derived peptide vaccines, vaccine combinations, rgp120 (AIDSVAX), ALVAC HIV (vCP1521)/AIDSVAX B/E (gp120) (RV144), monomeric gp120 HIV-1 subtype C vaccine (Novartis), Remune, ITV-1, Contre Vir, Ad5-ENVA-48, DCVax-001 (CDX-2401), PEP-6409,Vacc-4x, Vacc-C5, VAC-3S, multiclade DNA recombinant adenovirus-5 (rAd5), Pennvax-G, VRC-HIV MAB060-00-AB, AVX-101, Tat Oyi vaccine, AVX-201, HIV-LAMP-vax, Ad35, Ad35-GRIN, NAcGM3/VSSP ISA-51, poly-ICLC adjuvanted vaccines, TatImmune, GTU-multiHIV (FIT-06), AGS-004, gp140[delta]V2.TV1+ MF-59, rVSVIN HIV-1 gag vaccine, SeV-Gag vaccine, AT-20, DNK-4, Ad35-GRIN/ENV, TBC-M4, HIVAX , HIVAX-2, NYVAC-HIV-PT1, NYVAC-HIV-PT4, DNA-HIV-PT123,

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rAAV1-PG9DP, GOVX-B11, GOVX-B21, ThV-01, TUTI-16, VGX-3300, TVI-HIV-1, Ad-4 (Ad4-env Clade C + Ad4-mGag), EN41-UGR7C, EN41-FPA2, PreVaxTat, TL-01, SAV-001, AE-H, MYM-V101, CombiHIVvac, ADVAX, MYM-V201, MVA-CMDR, ETV-01, CDX-1401, rcAd26.MOS1.HIV-Env and DNA-Ad5 gag/pol/nef/nev (HVTN505);

(16) HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins (such as DARTs®, Duobodies®, Bites®, XmAbs®, TandAbs ®, Fab derivatives) including BMS-936559, TMB-360 and those targeting HIV gp120 or gp41 selected from the group consisting of bavituximab, UB-421, C2F5, C2G12, C4E10, C2F5+C2G12+C4E10, 3-BNC-117 , PGT145, PGT121, MDX010 (ipilimumab), VRC01, A32, 7B2, 10E8, VRC-07-523 and VRC07;

(17) latency reversing agents selected from the group consisting of Histone deacetylase inhibitors such as Romidepsin, vorinostat, panobinostat; Proteasome inhibitors such as Velcade; protein kinase C (PKC) activators such as Indolactam, Prostratin, Ingenol B and DAG-lactones, Ionomycin, GSK-343, PMA, SAHA, BRD4 inhibitors, IL-15, JQ1, disulfram, and amphotericin B;

(18) HIV nucleocapsid p7 (NCp7) inhibitors selected from the group consisting of azodicarbonamide;

(19) HIV maturation inhibitors selected from the group consisting of BMS-955176 and GSK-2838232;

(20) PI3K inhibitors selected from the group consisting of idelalisib, AZD-8186, buparlisib, CLR-457, pictilisib, neratinib, rigosertib, rigosertib sodium, EN-3342, TGR-1202, alpelisib, duvelisib, UCB-5857, taselisib, XL-765, gedatolisib, VS-5584, copanlisib, CAI orotate, perifosine, RG-7666, GSK-2636771, DS-7423, panulisib, GSK-2269557, GSK-2126458, CUDC-907, PQR-309, INCB-040093, pilaralisib, BAY-1082439, puquitinib mesylate, SAR-245409, AMG-319, RP-6530, ZSTK-474, MLN-1117, SF-1126, RV-1729, sonolisib, LY-3023414, SAR-260301 and CLR-1401;

(21) the compounds disclosed in WO 2004/096286 (Gilead Sciences), WO 2006/110157 (Gilead Sciences), WO 2006/015261 (Gilead Sciences), WO 2013/006738 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), US20140221380 (Japan Tobacco), US20140221378 (Japan Tobacco), WO 2013/006792 (Pharma Resources), WO

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2009/062285 (Boehringer Ingelheim), WO 2010/130034 (Boehringer Ingelheim), WO 2013/091096A1 (Boehringer Ingelheim), WO 2013/159064 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO2012/003497 (Gilead Sciences), WO2014/100323 (Gilead Sciences), WO2012/145728 (Gilead Sciences), WO2013/159064 (Gilead Sciences) and WO 2012/003498 (Gilead Sciences); and

(22) other drugs for treating HIV selected from the group consisting of BanLec, MK-8507, AG-1105, TR-452, MK-8591, REP 9, CYT-107, alisporivir, NOV-205, IND-02, metenkefalin, PGN-007, Acemannan, Gamimune, Prolastin, 1,5-dicaffeoylquinic acid, BIT-225, RPI-MN, VSSP, Hiviral, IMO-3100, SB-728-T, RPI-MN, VIR-576, HGTV-43, MK-1376, rHIV7-shl-TAR-CCR5RZ, MazF gene therapy, BlockAide, ABX-464, SCY-635, naltrexone, AAV-eCD4-Ig gene therapy and PA-1050040 (PA-040);

and combinations thereof.

[0206] In certain embodiments, a compound disclosed herein is combined with two, three, four or more additional therapeutic agents. In certain embodiments, a compound disclosed herein is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein is combined with four additional therapeutic agents. The two, three four or more additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, or they can be selected from different classes of therapeutic agents. In a specific embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In a further embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer. In another embodiment, a compound disclosed herein is combined with two HIV nucleoside or nucleotide inhibitors of reverse transcriptase.

[0207] In certain embodiments, a compound disclosed herein, is combined with one, two, three, four or more additional therapeutic agents. In certain embodiments, a compound disclosed herein is combined with one additional therapeutic agent. In certain embodiments, a compound disclosed herein is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein is combined with four additional therapeutic agents. The one, two, three, four or more additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, and/or they can be selected from different classes of therapeutic agents. In a specific embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In a further embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer. In certain embodiments, a compound disclosed herein is combined with at least one HIV nucleoside inhibitor of reverse transcriptase, an integrase inhibitor, and a pharmacokinetic enhancer. In another embodiment, a compound disclosed herein is combined with two HIV nucleoside or nucleotide inhibitors of reverse transcriptase.

[0208] In certain embodiments, a compound disclosed herein is combined with at least one HIV nucleoside inhibitor of reverse transcriptase, an integrase inhibitor, and a pharmacokinetic enhancer.

[0209] In a particular embodiment, a compound disclosed herein is combined with abacavir, abacavir sulfate, tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

[0210] In a particular embodiment, a compound disclosed herein is combined with tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

[0211] In a particular embodiment, a compound disclosed herein is combined with a first additional therapeutic agent selected from the group consisting of: abacavir, abacavir sulfate, tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate and a second additional therapeutic agent selected from the group consisting of emtricitibine and lamivudine.

[0212] In a particular embodiment, a compound disclosed herein is combined with a first additional therapeutic agent selected from the group consisting of: tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitibine.

[0213] In a particular embodiment, a compound disclosed herein is combined with one, two, three, four or more additional therapeutic agents selected from Triumeq® (dolutegravir+abacavir +lamivudine), dolutegravir + abacavir sulfate + lamivudine, raltegravir, raltegravir + lamivudine, Truvada® (tenofovir disoproxil fumarate +emtricitabine, TDF+FTC), maraviroc, enfuvirtide , Epzicom® (Livexa®, abacavir sulfate +lamivudine, ABC+3TC), Trizivir® (abacavir sulfate+zidovudine+lamivudine, ABC+AZT+3TC), adefovir, adefovir dipivoxil, Stribild ® (elvitegravir+cobicistat+tenofovir disoproxil fumarate +emtricitabine), rilpivirine, rilpivirine hydrochloride, Complera® (Eviplera®, rilpivirine+tenofovir disoproxil fumarate +emtricitabine), Cobicistat, atazanavir sulfate + cobicistat, atazanavir + cobicistat, darunavir + cobicistat, Atripla® (efavirenz+tenofovir disoproxil fumarate +emtricitabine), atazanavir, atazanavir sulfate, dolutegravir, elvitegravir, Aluvia® (Kaletra®, lopinavir+ritonavir), ritonavir , emtricitabine , atazanavir sulfate + ritonavir, darunavir, lamivudine, Prolastin, fosamprenavir, fosamprenavir calcium, efavirenz, Combivir® (zidovudine+lamivudine, AZT+3TC), etravirine, nelfinavir, nelfinavir mesylate, interferon, didanosine, stavudine, indinavir, indinavir sulfate, tenofovir + lamivudine, zidovudine, nevirapine, saquinavir, saquinavir mesylate, aldesleukin, zalcitabine, tipranavir, amprenavir, delavirdine, delavirdine mesylate, Radha-108 (Receptol), Hlviral, lamivudine + tenofovir disoproxil fumarate, efavirenz + lamivudine + tenofovir disoproxil fumarate , phosphazid, lamivudine + nevirapine + zidovudine, abacavir, abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, darunavir + cobicistat, atazanavir sulfate + cobicistat, atazanavir + cobicistat, tenofovir alafenamide and tenofovir alafenamide hemifumarate.

[0214] In a particular embodiment, a compound disclosed herein is combined with abacavir, abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide or tenofovir alafenamide hemifumarate.

[0215] In a particular embodiment, a compound disclosed herein is combined with tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

[0216] In a particular embodiment, a compound disclosed herein is combined with a first additional therapeutic agent selected from the group consisting of: abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate and a second additional therapeutic agent selected from the group consisting of emtricitabine and lamivudine.

[0217] In a particular embodiment, a compound disclosed herein is combined with a first additional therapeutic agent selected from the group consisting of: tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine.

[0218] In certain embodiments, a compound disclosed herein is combined with 5-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 5-10; 5-15; 5-20; 5-25; 25-30; 20-30; 15-30; or 10-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 10 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of Formulas (I), (II), and/or (III)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 50 mg to 500 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[0219] In certain embodiments, a compound disclosed herein is combined with 200-400 mg tenofovir disproxil, tenofovir disoproxil fumarate, or tenofovir disoproxil hemifumarate and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 200-250; 200-300; 200-350; 250-350; 250-400; 350-400; 300-400; or 250-400 mg tenofovir disoproxil, tenofovir disoproxil fumarate, or tenofovir disoproxil hemifumarate and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 300 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of Formulas (I), (II), and/or (III)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 50 mg to 500 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[0220] In certain embodiments, when a compound disclosed herein is combined with one or more additional therapeutic agents as described above, the components of the composition are administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

[0221] In certain embodiments, a compound disclosed herein is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a patient, for example as a solid dosage form for oral administration.

[0222] In certain embodiments, a compound disclosed herein is administered with one or more additional therapeutic agents. Co-administration of a compound disclosed herein with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein and one or more additional therapeutic agents, such that therapeutically effective amounts of the compound disclosed herein and one or more additional therapeutic agents are both present in the body of the patient.

[0223] Co-administration includes administration of unit dosages of the compounds disclosed herein before or after administration of unit dosages of one or more additional therapeutic agents, for example, administration of the compound disclosed herein within seconds, minutes, or hours of the administration of one or more additional therapeutic agents. For example, in some embodiments, a unit dose of a compound disclosed herein is administered first, followed within seconds or minutes by administration of a unit dose of one

or more additional therapeutic agents. Alternatively, in other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound disclosed herein within seconds or minutes. In some embodiments, a unit dose of a compound disclosed herein is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound disclosed herein.

XRPD Data

[0224] In certain embodiments, the crystalline forms are characterized by the interlattice plane intervals determined by an X-ray powder diffraction pattern (XRPD). The diffractogram of XRPD is typically represented by a diagram plotting the intensity of the peaks versus the location of the peaks, i.e., diffraction angle 2θ (two-theta) in degrees. The intensities are often given in parenthesis with the following abbreviations: very strong = vst; strong = st; medium = m; weak = w; and very weak = vw. The characteristic peaks of a given XRPD can be selected according to the peak locations and their relative intensity to conveniently distinguish this crystalline structure from others.

[0225] Those skilled in the art recognize that the measurements of the XRPD peak locations and/or intensity for a given crystalline form of the same compound will vary within a margin of error. The values of degree 2θ allow appropriate error margins. Typically, the error margins are represented by "±". For example, the degree 2θ of about "8.7±0.3" denotes a range from about 8.7+0.3, i.e., about 9.0, to about 8.7-0.3, i.e., about 8.4. Depending on the sample preparation techniques, the calibration techniques applied to the instruments, human operational variation, and etc, those skilled in the art recognize that the appropriate error of margins for a XRPD can be ±0.5; ±0.4; ±0.3; ±0.2; ±0.1; ±0.05; or less. In certain embodiments of the invention, the XRPD margin of error is ±0.2.

[0226] Additional details of the methods and equipment used for the XRPD analysis are described in the Examples section.

[0227] The XRPD peaks for the crystalline forms of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-

methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (Formula I) Form I is below in Table 1A.

Table 1A: XRPD peaks for crystalline forms of Formula I Form I

Formula I Form I	
Peak Position [°2θ]	Relative Intensity [%]
9.3	6.4
10.5	43.7
11.4	12.6
13.1	96.7
13.9	33.0
16.2	79.4
17.4	48.0
20.6	93.1
22.3	42.0
25.0	81.5
27.4	100.0

[0228] The XRPD peaks for the crystalline form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (Formula I) Form II is below in Table 1B.

Table 1B: XRPD peaks for crystalline forms of Formula I Form II

Formula I Form II	
Peak Position [°2θ]	Relative Intensity [%]
6.6	100.0
10.6	59.3
12.5	30.6
14.3	14.9
16.2	19.3
21.4	65.1
23.5	10.6
25.6	11.9

[0229] The XRPD peaks for the crystalline form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (Formula I) Form III is below in Table 1C.

Table 1C: XRPD peaks for crystalline forms of Formula I Form III

Formula I Form III	
Peak Position [°2θ]	Relative Intensity [%]
9.6	56.7
12.1	19.1
14.0	26.2
16.2	17.6
18.5	74.6
20.0	100.0
22.5	35.4
25.0	19.2
27.0	18.0
29.0	14.0

[0230] The XRPD peaks for the crystalline form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-

methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (Formula I) Form IV is below in Table 1D.

Table 1D: XRPD peaks for crystalline forms of Formula I Form IV

Formula I Form IV	
Peak Position [°2θ]	Relative Intensity [%]
6.2	96.1
8.6	40.0
13.2	22.0
16.3	100.0
18.7	32.7
20.0	33.1
22.3	72.9
22.7	76.2
25.8	44.1
27.7	30.3

[0231] The XRPD peaks for the crystalline form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate (Formula II) is below in Table 1E.

Table 1E: XRPD peaks for crystalline forms of Formula II Form I

Formula II Form I	
Peak Position [°2θ]	Relative Intensity [%]
5.5	100.0
16.1	87.3
17.9	22.4
19.5	38.0
22.1	61.8
22.5	42.2
23.3	60.4
26.6	27.3
28.5	42.9

[0232] The XRPD peaks for the crystalline form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide oxalic acid co-crystal Form I is below in Table 1F.

Table 1F: XRPD peaks for crystalline forms of Formula I Oxalic Acid Co-crystal Form I

Formula I Oxalic Acid Co-crystal Form I	
Peak Position [°2θ]	Relative Intensity [%]
7.6	16.5
9.1	39.4
11.6	13.6
14.5	94.8
17.1	51.1
19.1	100.0
21.8	40.7
26.5	54.8
29.7	30.4
39.4	37.1

Preparation of the Polymorphs

Formula I

[0233] One method of synthesizing (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (*e.g.* a compound of Formula (I)) has been previously described in PCT Publication No. WO2014/100323. This reference is hereby incorporated herein by reference in its entirety, and specifically with respect to the synthesis of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide.

[0234] For example, in one aspect, provided is a method of producing a composition comprising one or more polymorphs of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-

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b][1,3]oxazepine-10-carboxamide, wherein the method comprises combining a compound of Formula (I) with a suitable solvent or a mixture of suitable solvents to produce a composition comprising one or more polymorphs of the compound of Formula (I). In another aspect, provided is another method of producing a composition comprising one or more polymorphs of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the method comprises combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a suitable solvent or a mixture of suitable solvents.

[0235] The choice of a particular solvent or combination of solvents affects the formation favoring one polymorphic form of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide over another. Solvents suitable for polymorph formation may include, for example, methanol, ethanol, water, isopropyl acetate, acetonitrile, tetrahydrofuran, methyl isobutyl ketone, and any mixtures thereof.

[0236] In another aspect, provided is also one or more polymorphs of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide produced according to any of the methods described herein.

[0237] It should be understood that the methods for preparing the polymorphs described herein (including any one or more of polymorphic Forms I to VIII) may yield quantity and quality differences compared to the methods for preparing (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide produced on laboratory scale.

Formula I, Forms I and II

[0238] In one embodiment, provided is a method of producing a composition comprising polymorphic Form I, Form II, or a mixture thereof, of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the method

comprises combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a solvent to produce a composition comprising polymorphic Form I, Form II, or a mixture thereof, of the (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the solvent is isopropyl acetate.

[0239] Provided is a polymorphic Form I, Form II, or a mixture thereof, of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide produced by combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a solvent, wherein the solvent is isopropyl acetate.

Formula I, Form III

[0240] In one embodiment, provided is a method of producing a composition comprising polymorphic Form III of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the method comprises combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a solvent to produce a composition comprising polymorphic Form III of the (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the solvent is methyl isobutyl ketone.

[0241] Provided is a polymorphic Form III of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide produced by combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a solvent, wherein the solvent is methyl isobutyl ketone.

Formula I, Forms IV, VII, and VIII

[0242] In one embodiment, provided is a method of producing a composition comprising polymorphic Form IV, Form VII, and Form VIII, or a mixture thereof, of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the method comprises combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a solvent to produce a composition comprising polymorphic Form IV, Form VII, and Form VIII, or a mixture thereof, of the (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the solvent is methanol.

[0243] Provided is a polymorphic Form IV, Form VII, and Form VIII, or a mixture thereof, of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide produced by combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a solvent, wherein the solvent is methanol.

Formula I, Form V

[0244] In one embodiment, provided is a method of producing a composition comprising polymorphic Form V of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the method comprises combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a solvent to produce a composition comprising polymorphic Form V of the (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the solvent is water.

[0245] Provided is a polymorphic Form V of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-

(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide produced by combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a solvent, wherein the solvent is water.

Formula I, Form VI

[0246] In one embodiment, provided is a method of producing a composition comprising polymorphic Form VI of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the method comprises combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a solvent to produce a composition comprising polymorphic Form VI of the (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the solvent is selected from the group consisting of methanol, water, and any mixtures thereof. In an embodiment, the solvent is a mixture of water and methanol.

[0247] Provided is a polymorphic Form VI of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide produced by combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a solvent, wherein the solvent is selected from the group consisting of methanol, water, and any mixtures thereof. In an embodiment, the solvent is a mixture of water and methanol.

Formula II

[0248] One method of synthesizing (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (*e.g.* a compound of Formula (I)) has been previously described in PCT Publication No. WO2014/100323. This reference is hereby incorporated herein by reference in its entirety, and specifically with respect to the synthesis of

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(2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide. One method of synthesizing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate (*e.g.* a compound of Formula (II)) is described herein.

[0249] For example, in one aspect, provided is a method of producing a composition comprising one or more polymorphs of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the method comprises combining a compound of Formula (II) with a suitable solvent or a mixture of suitable solvents to produce a composition comprising one or more polymorphs of the compound of Formula (II). In another aspect, provided is another method of producing a composition comprising one or more polymorphs of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the method comprises combining sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate with a suitable solvent or a mixture of suitable solvents.

[0250] The choice of a particular solvent or combination of solvents affects the formation favoring one polymorphic form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate over another. Solvents suitable for polymorph formation may include, for example, methanol, ethanol, water, isopropyl acetate, acetonitrile, tetrahydrofuran, methyl isobutyl ketone, and any mixtures thereof.

[0251] In another aspect, provided is also one or more polymorphs of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate produced according to any of the methods described herein.

[0252] It should be understood that the methods for preparing the polymorphs described herein (including any polymorphic Form I) may yield quantity and quality differences compared to the methods for preparing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-

trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate produced on laboratory scale.

Formula II, Form I

[0253] In one embodiment, provided is a method of producing a composition comprising polymorphic Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the method comprises combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a sodium base (*e.g.* sodium hydroxide) in a solvent to produce a composition comprising polymorphic Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the solvent is selected from the group consisting of ethanol, dimethylformamide, and any mixture thereof. In an embodiment, the solvent is a mixture of ethanol and dimethylformamide.

[0254] Provided is also polymorphic Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate prepared by combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a sodium base (*e.g.* sodium hydroxide) in a solvent, wherein the solvent is selected from the group consisting of ethanol, dimethylformamide, and any mixture thereof. In an embodiment, the solvent is a mixture of ethanol and dimethylformamide.

Formula III

[0255] One method of synthesizing (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (*e.g.* a compound of Formula (I)) has been previously described in PCT Publication No. WO2014/100323. This reference is hereby incorporated herein by reference in its entirety, and specifically with respect to the synthesis of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-

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2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide. One method of synthesizing potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate (*e.g.* a compound of Formula (III)) is described herein.

[0256] For example, in one aspect, provided is a method of producing a composition comprising one or more polymorphs of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the method comprises combining a compound of Formula (III) with a suitable solvent or a mixture of suitable solvents to produce a composition comprising one or more polymorphs of the compound of Formula (III). In another aspect, provided is another method of producing a composition comprising one or more polymorphs of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the method comprises combining potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate with a suitable solvent or a mixture of suitable solvents.

[0257] The choice of a particular solvent or combination of solvents affects the formation favoring one polymorphic form of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate over another. Solvents suitable for polymorph formation may include, for example, methanol, ethanol, water, isopropyl acetate, acetonitrile, tetrahydrofuran, methyl isobutyl ketone, and any mixtures thereof.

[0258] In another aspect, provided is also one or more polymorphs of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate produced according to any of the methods described herein.

[0259] It should be understood that the methods for preparing the polymorphs described herein (including any one or more of polymorphic Forms I-III) may yield quantity and quality differences compared to the methods for preparing potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-

methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate produced on laboratory scale.

Formula III, Form I

[0260] In one embodiment, provided is a method of producing a composition comprising polymorphic Form I of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the method comprises combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a potassium base (*e.g.* potassium acetate) in a solvent to produce a composition comprising polymorphic Form I of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the solvent is selected from the group consisting of ethanol, water, and any mixtures thereof. In an embodiment, the solvent is a mixture of ethanol and water.

[0261] Provided is also polymorphic Form I of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate prepared by combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a potassium base (*e.g.* potassium acetate) in a solvent, wherein the solvent is selected from the group consisting of ethanol, water, and any mixtures thereof.

Formula III, Form II

[0262] In one embodiment, provided is a method of producing a composition comprising polymorphic Form II of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the method comprises combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a potassium base (*e.g.* potassium acetate) in a solvent to produce a composition comprising polymorphic Form II of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-

trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the solvent is selected from the group consisting of acetonitrile, water, and any mixtures thereof. In an embodiment, the solvent is a mixture of acetonitrile and water.

[0263] Provided is also polymorphic Form II of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate prepared by combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a potassium base (*e.g.* potassium acetate) in a solvent, wherein the solvent is selected from the group consisting of acetonitrile, water, and any mixtures thereof.

Formula III, Form III

[0264] In one embodiment, provided is a method of producing a composition comprising polymorphic Form III of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the method comprises combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a potassium base (*e.g.* potassium phosphate) in a solvent to produce a composition comprising polymorphic Form III of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the solvent is methanol.

[0265] Provided is also polymorphic Form III of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate prepared by combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a potassium base (*e.g.* potassium phosphate) in a solvent, wherein the solvent is methanol.

Formula I Co-Crystals

[0266] In one embodiment, provided is a method of producing a composition comprising polymorphic citric acid co-crystal, fumaric acid co-crystal, oxalic acid co-crystal, or a mixture thereof, of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the method comprises combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with an acid (*e.g.* citric acid, fumaric acid, or oxalic acid) in a solvent to produce a composition comprising polymorphic citric acid co-crystal, fumaric acid co-crystal, oxalic acid co-crystal, or a mixture thereof, of the (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the solvent is tetrahydrofuran.

[0267] Provided is a polymorphic citric acid co-crystal, fumaric acid co-crystal, oxalic acid co-crystal, or a mixture thereof, of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide produced by combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with an acid (*e.g.* citric acid, fumaric acid, or oxalic acid) in a solvent, wherein the solvent is tetrahydrofuran.

Uses in Manufacturing of Drug Product

Formula I

[0268] Provided are also a use of the polymorphs described herein in the manufacture of a drug product. The one or more of the polymorphic forms described herein (*e.g.*, one or more of polymorphic Forms I, II, III, IV, V, VI, VII, and VIII) may be used as an intermediate in the manufacturing process to produce the drug product.

[0269] In certain embodiments, Forms I to VIII of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide are used in the

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manufacture of an active pharmaceutical ingredient. In certain embodiments, Form I of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide is used in the manufacture of an active pharmaceutical ingredient. In certain embodiments, Form II of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide is used in the manufacture of an active pharmaceutical ingredient. In certain embodiments, Form III of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide is used in the manufacture of an active pharmaceutical ingredient. In certain embodiments, Form IV of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide is used in the manufacture of an active pharmaceutical ingredient. In certain embodiments, Form V of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide is used in the manufacture of an active pharmaceutical ingredient. In certain embodiments, Form VI of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide is used in the manufacture of an active pharmaceutical ingredient. In certain embodiments, Form VII of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide is used in the manufacture of an active pharmaceutical ingredient. In certain embodiments, Form VIII of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamideis used in the manufacture of an active pharmaceutical ingredient.

Formula II

[0270] Provided are also a use of the polymorphs described herein in the manufacture of a drug product. The one or more of the polymorphic forms described herein (*e.g.*, polymorphic Form I) may be used as an intermediate in the manufacturing process to produce the drug product.

[0271] In certain embodiments, Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-

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methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate are used in the manufacture of an active pharmaceutical ingredient.

Formula III

[0272] Provided are also a use of the polymorphs described herein in the manufacture of a drug product. The one or more of the polymorphic forms described herein (*e.g.*, one or more of polymorphic Forms I, II, and III) may be used as an intermediate in the manufacturing process to produce the drug product.

[0273] In certain embodiments, Forms I-III of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate are used in the manufacture of an active pharmaceutical ingredient. In certain embodiments, Form I of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate is used in the manufacture of an active pharmaceutical ingredient. In certain embodiments, Form II of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate is used in the manufacture of an active pharmaceutical ingredient. In certain embodiments, Form III of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate is used in the manufacture of an active pharmaceutical ingredient.

Articles of Manufacture and Kits

[0274] Compositions comprising one or more of the polymorphic forms described herein (*e.g.*, one or more of polymorphic Forms I to VIII of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide; polymorphic Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate; and polymorphic Forms I, II, and III of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate) and formulated in one or more

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pharmaceutically acceptable carriers, excipients or other ingredients can be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition. Accordingly, there also is contemplated an article of manufacture, such as a container comprising a dosage form of one or more of the polymorphic forms described herein (*e.g.*, one or more of polymorphic Forms I to VIII of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide; polymorphic Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate; and polymorphic Forms I, II, and III of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate), and a label containing instructions for use of the compound*(s)*.

[0275] In some embodiments, the article of manufacture is a container comprising a dosage form of one or more of the polymorphic forms described herein (*e.g.*, one or more of polymorphic Forms I to VIII of (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide; polymorphic Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate; and polymorphic Forms I, II, and III of potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate), and one or more pharmaceutically acceptable carriers, excipients or other ingredients. In one embodiment of the articles of manufacture described herein, the dosage form is a tablet.

[0276] Kits also are contemplated. For example, a kit can comprise a dosage form of a pharmaceutical composition and a package insert containing instructions for use of the composition in treatment of a medical condition. The instructions for use in the kit may be for treating HIV. In certain embodiments, the instructions for use in the kit may be for treating HIV.

[0277] In certain embodiments, the polymorphic, salt, co-crystal and solvate forms described herein may potentially exhibit improved properties. For example, in certain embodiments, the polymorphic, salt, co-crystal and solvate forms described herein may

potentially exhibit improved stability. Such improved stability could have a potentially beneficial impact on the manufacture of the Compound of Formulas I, II, and/or III, such as for example offering the ability to store process intermediate for extended periods of time. Improved stability could also potentially benefit a composition or pharmaceutical composition of the Compound of Formulas I, II, and/or III. In certain embodiments, the polymorphic, salt and solvate forms described herein may also potentially result in improved yield of the Compound of Formulas I, II, and/or III, or potentially result in an improvement of the quality of the Compound of Formulas I, II, and/or III. In certain embodiments, the polymorphic, salt and solvate forms described herein may also exhibit improved pharmacokinetic properties and/or potentially improved bioavailability.

Methods

Formula I Form I

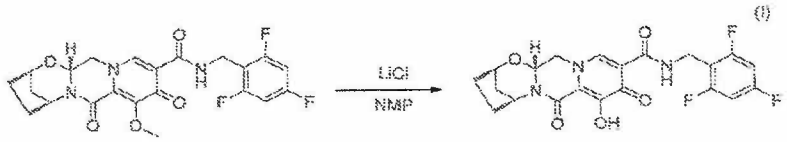
[0278] (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (73 mg) was added to a glass vial. Isopropanol (1 mL) was added, the vial was capped, and the suspension was stirred at about 21 °C for not less than 5 days. Formula I Form I was isolated as a solid from the suspension by centrifuge/filtration and characterized as discussed below.

Formula I Form II

[0279] (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (60 mg) was added to a glass vial. Methyl tert-butyl ether (1 mL) was added, the vial was capped, and the suspension was stirred at about 21 °C for not less than 5 days. Formula I Form II was isolated as a solid from the suspension by centrifuge/filtration and characterized as discussed below.

[0280] (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (98 mg) was suspended in ethanol/water (1 mL, aw 0.7-0.8) for 5 days with agitation. Formula I Form II was isolated as a solid from the suspension by centrifuge/filtration and characterized as discussed below.

Formula I Form III from Compound G-1a



Compound G1-a

[0281] A solution of about 10% (w/w) Compound G-1a (2.5 g Compound 1001) in methylene chloride was concentrated to a residue under vacuum. LiCl (2.6 g, 7 equiv) followed by *N*-methyl-2-pyrrolidone (12.5 mL) was added to the resulting residue. The method of preparing compound G1-a can be determined by one skilled on the art, for example, as described in co-pending PCT Serial No. US2013/076367, filed December 19, 2013 entitled, "POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE." The mixture was heated to an internal temperature of approximately 75 °C. After 2.5 hours, the reaction was cooled to approximately 20 °C. Dichloromethane (12.5 mL) and 0.5M hydrochloric acid (12.5 mL) was added, and the resulting mixture stirred for 5 minutes. The phases were separated, and the organic layer was washed with 10% aqueous sodium chloride solution (twice) followed by water. This solution was concentrated while gradually adding 3 volumes of isopropyl alcohol portionwise (40 °C bath temperature, 200-230 torr vacuum). The resulting slurry was slowly cooled to 2-4 °C. The product was filtered and deliquored and dried. Formula I Form III was isolated and characterized as discussed below.

Formula I Form III from Formula I

[0282] (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (100mg) and ethanol (0.5 mL) were added to a reaction vessel and seeded with Formula I Form III. The slurry was allowed to age at room temperature for about 18 hours. Formula I Form III was isolated as a solid from the suspension by centrifuge/filtration and characterized as discussed below.

Formula I Form IV

[0283] (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (406 mg) and potassium acetate (200 mg) were added to a glass vial. Methanol (5 mL) was added, the vial was capped, and the suspension was stirred at about 21 °C. After 11 days the solids were isolated from the suspension by centrifuge/filtration and the filtrate retained. After slow evaporation over 16 days, large crystals of Formula I Form IV were found in the filtrate vessel.

Formula I Form V

[0284] 25.2 mg (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (25.2 mg) was mixed with 1.21 grams of water at room temperature, forming a solution. After several days, crystals suitable for single crystal X-ray crystallography were found and analyzed.

Formula I Form VI

[0285] 173 mg of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (25.2 mg) was suspended in 2 mL of methanol/water solution (a_w 0.5). The suspension was filtered the next day and several days after that, crystals suitable for single crystal X-ray crystallography were found in the filtrate and analyzed.

Formula I Form VII

[0286] 112.3 mg (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (25.2 mg) suspended in 0.95 grams of methanol at room temperature. A sample of the suspension was filtered for testing after several days, and several days post-filtration, solids suitable for single crystal X-ray crystallography were found in the filtrate and analyzed.

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Formula I Form VIII

[0287] 5.3 g (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (25.2 mg) suspended in 80 mL of methanol at room temperature. To the mixture was slowly added 0.70 grams of KOH dissolved in 20 mL methanol. Full addition of KOH solution resulted in a solution. A suspension formed over the course of two days and a sample was filtered for testing after ten days. After several days, solids suitable for single crystal X-ray crystallography were found in the filtrate and analyzed.

Formula II Form I

[0288] (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (20 g) and ethanol (80 mL) were added to a reaction vessel and warmed to about 75 °C. Aqueous sodium hydroxide (22 mL 2 M solution) was added over approximately 30 minutes, after which the slurry was cooled to approximately 20 °C over approximately one hour. Sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was collected by filtration, washed with EtOH (50 mL) and dried under vacuum.

[0289] 1H NMR (400 MHz, DMSO-d6) δ 10.63 (t, J = 5.8 Hz, 1H), 7.88 (s, 1H), 7.29 – 7.07 (m, 2H), 5.20 (dd, J = 8.6, 3.6 Hz, 1H), 5.09 (t, J = 4.1 Hz, 1H), 4.52 (m, 3H), 4.35 (dd, J = 12.8, 3.6 Hz, 1H), 3.87 (dd, J = 12.7, 8.7 Hz, 1H), 2.03 – 1.80 (m, 3H), 1.76-1.64 (m, 2H), 1.50 – 1.40 (m, 1H).

Formula I Citric Acid Co-crystal Form I

[0290] (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (131 mg) and citric acid (148 mg) were added to a glass vial. Tetrahydrofuran (1 mL) was added, the vial was capped, and the mixture was stirred at about 21 °C for two days. The vial was vented and the solvent was allowed to evaporate at about 21 °C unassisted. After eight weeks at room temperature, crystals were found in the vessel and were identified as a 1:2 Formula I citric acid co-crystal.

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Formula I Fumaric Acid Co-crystal Form I

[0291] (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (131 mg) and fumaric acid (103 mg) were added to a glass vial. Tetrahydrofuran (1 mL) was added, the vial capped, and the suspension stirred at about 21 °C for two days. An additional 1 mL of tetrahydrofuran was added, and the mixture was heated to 45 °C. After about 12 hours at 45 °C the mixture was found to be fully dissolved and was removed from the heat bath. The vial was vented, and the solvent left to evaporate at room temperature. After one day solids were observed in the vial and it was re-capped. After eight weeks large crystals were found in the capped vial and identified as a 1:1 Formula I fumaric acid co-crystal.

Formula I Oxalic Acid Co-crystal Form I

[0292] (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (147 mg) and oxalic acid (134 mg) were added to a glass vial. Tetrahydrofuran (1 mL) was added, the vial capped, and the resulting solution was stirred at about 21 °C for about two days. The vessel was vented, and the solvent was allowed to evaporate at room temperature unassisted. After one day solids were observed in the vial and it was re-capped. Two days later large crystals were found in the vial and were identified as a 1:1 Formula I oxalic acid co-crystal.

Formula III Form I

[0293] 406 mg of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (25.2 mg) was combined with 200 mg potassium acetate and 5 mL of methanol at room temperature, resulting in a suspension. A sample of the suspension was filtered the next day for testing. After several days, solids suitable for single crystal X-ray crystallography were found in the filtrate and analyzed.

[0294] (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (1.96 g) was charged to a reaction flask and stirred, followed by ethanol (20 mL). The mixture was stirred at room temperature resulting in a suspension. In a separate vessel potassium

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hydroxide (253 mg) was dissolved in deionized water (5 mL). The potassium hydroxide solution was transferred by syringe pump to the stirring suspension over about 2.5 hours followed by a rinse into the reactor with water (2 mL) after the base solution transfer was completed.

[0295] A sample of about 0.5 mL of the resulting suspension was centrifuge/filtered. The filtrate was retained and stored at room temperature. After several weeks it had evaporated and the vessel contained large crystals, which were identified by single x-ray crystallography as Formula III Form II.

Formula III Form II (Dimer)

[0296] 94.8 mg of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (25.2 mg) was suspended in 1 mL of acetonitrile/water (1:1). After one week a sample was filtered for testing. After several days, solids suitable for single crystal X-ray crystallography were found in the filtrate and analyzed.

Formula III Form III

[0297] A 4 mL glass vial was charged with 140 mg of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, and 73 mg of potassium phosphate and 2 mL of methanol. The vial was capped and placed in a rotating mixer to provide gentle and constant mixing. The experiment was carried out at room temperature. More than a week later and more than a month later solids were isolated by centrifuge/filtration and examined by XRPD. Large crystals suitable for Single Crystal X-ray Crystallography were found and analyzed.

[0298] The crystalline forms of the present invention were characterized by various analytical techniques, including X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and dynamic vapor sorption (DVS) using the procedures described below.

[0299] *X-Ray Powder Diffraction*: XRPD analysis was conducted on a diffractometer

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(PANanalytical XPERT-PRO, PANanalytical B.V., Almelo, Netherlands) using copper radiation (Cu Kα, λ = 1.5418 Å). Samples were prepared for analysis by depositing the powdered sample in the center of an aluminum holder equipped with a zero background plate. The generator was operated at a voltage of 45 kV and amperage of 40 mA. Slits used were Soller 0.02 rad., antiscatter 1.0°, and divergence. The sample rotation speed was 2 sec. Scans were performed from 2 to 40° 2θ during 15 min with a step size of 0.0167° 2θ. Data analysis was performed by X'Pert Highscore version 2.2c (PANalytical B.V., Almelo, Netherlands) and X'Pert data viewer version 1.2d (PANalytical B.V., Almelo, Netherlands).

[0300] The XRPD pattern for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form I is represented in Figure 1.

[0301] The XRPD pattern for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form II is represented in Figure 2.

[0302] The XRPD pattern for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form III is represented in Figure 3.

[0303] The XRPD pattern for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form IV is represented in Figure 4.

[0304] The XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is represented in Figure 5. The calculated XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I represented in Figure 5 was calculated by using Mercury 3.1 Development (Build RC5). Single crystal data for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was input into Mercury 3.1 Development (Build RC5) to calculate the XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-

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2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I. Bulk material, such as stoichiometry arity between the temperature was obtained on a Rigaku Miniflex II XRD using power settings of 40kV, 15mA, scan speed of 2.0000 degrees per minute, a Miniflex 300/600 goniometer and an ASC-6 attachment, a scan range of 3.000 to 40.000 degrees, an incident slit of 1.250 degress, a length limiting slit of 10.0 mm, and SC-70 detector, a receiving slit #1 of 1.250 degrees, continuous scan mode, and a receiving slit #2 of 0.3mm. The sample was prepared by smoothing about 20 mg of solids on a silicon disk mounted in a metal holder. Acquisition temperature was ~21 °C.

[0305] The XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is further represented in Figure 16. The calculated XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I represented in Figure 16 was calculated by using Mercury 3.1 Development (Build RC5). Single crystal data for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was input into Mercury 3.1 Development (Build RC5) to calculate the XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I. Bulk material, such as stoichiometry arity between the temperature was obtained on a Rigaku Miniflex II XRD using power settings of 40kV, 15mA, scan speed of 2.0000 degrees per minute, a Miniflex 300/600 goniometer and an ASC-6 attachment, a scan range of 3.000 to 40.000 degrees, an incident slit of 1.250 degress, a length limiting slit of 10.0 mm, and SC-70 detector, a receiving slit #1 of 1.250 degrees, continuous scan mode, and a receiving slit #2 of 0.3mm. The sample was prepared by smoothing about 20 mg of solids on a silicon disk mounted in a metal holder. Acquisition temperature was ~21 °C.

[0306] Figure 16 compares the calculated XRPD pattern of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I to the experimental XRPD pattern of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-

olate Form I. The comparison shows the degree to which the calculated XRPD and experimental XRPD agree. Strong agreement indicates the solved crystal structure is also the crystal structure of the material analyzed directly by XRPD. This determination can support orthogonal data about the composition of the bulk material, such as stoichiometry.

[0307] The actual and calculated XRPD pattern for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide oxalic acid co-crystal Form I is represented in Figure 6.

[0308] *Differential scanning calorimetry*: Thermal properties were evaluated using a Differential Scanning Calorimetry (DSC) instrument (TA Q1000, TA Instruments, New Castle, DE, USA). Approximately 1 to 10 mg of solid sample was placed in a standard aluminum pan vented with a pinhole for each experiment and heated at a rate of 5 to 10 °C/min under a 50 mL/min nitrogen purge. Data analysis was conducted using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE, USA). Heat of fusion analysis was conducted by sigmoidal integration of the endothermic melting peak.

[0309] The DSC for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form I is represented in Figure 7.

[0310] The DSC for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form III is represented in Figure 8.

[0311] The DSC for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is represented in Figure 9.

[0312] *Thermogravimetric analysis*: Thermogravimetric analysis (TGA) was performed on a TGA instrument (TA Q500, TA Instruments, New Castle, DE, USA). Approximately 1 to 10 mg of solid sample was placed in an open aluminum pan for each experiment and heated at a rate of 5 to 10 °C/min under a 60 mL/min nitrogen purge using. Data analysis was conducted using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE,

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USA).

[0313] The TGA for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form I is represented in Figure 10.

[0314] The TGA for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form III is represented in Figure 11.

[0315] The TGA for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is represented in Figure 12.

[0316] *Dynamic vapor sorption*: The hygroscopicity was evaluated at room temperature using a dynamic vapor sorption (DVS) instrument (TGA Q5000 TA Instruments, New Castle, DE). Water adsorption and desorption were studied as a function of relative humidity (RH) over the range of 0 to 90% at 25 °C. The relative humidity in the chamber was increased by 10% RH and held until the so lid and atmosphere reached equilibration. The equilibrium test was continued until passed or expired after 5 or 10 hours. At this point, RH was raised 10% higher and the process was repeated until 90% RH was reached and equilibrated. During this period, the water sorption was monitored. For desorption, the relative humidity was decreased in a similar manner to measure a full sorption/desorption cycle. The cycle was optionally repeated. All experiments were operated in dm/dt mode (mass variation over time) to determine the equilibration endpoint. Approximately 5-10 mg of solid was used. Data analysis was conducted using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE, USA).

[0317] The DVS for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form I is represented in Figure 13.

[0318] The DVS for (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form III is represented in Figure 14.

[0319] The DVS for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is represented in Figure 15.

[0320] The single crystal X-ray diffraction studies were carried out on a Bruker APEX II Ultra diffractometer equipped with Mo K_α radiation (*e.g.* Wavelength). Crystals of the subject compound were cut into a 0.22 x 0.18 x 0.04 mm section and mounted on a Cryoloop with Paratone-N oil. Data were collected in a nitrogen gas stream at a particular temperature as shown in the Tables below (*e.g.* 100(2) K or 200(2) K). A total number of reflections were collected covering the indices, (*e.g.* -9<=*h*<=10, -13<=*k*<=16, -37<=*l*<=36). Certain reflections were found to be symmetry independent, with a R_{int} value. Indexing and unit-cell refinement indicated a crystal system (*e.g.* monoclinic, triclinic, or orthorhombic lattice). The space group, which was uniquely defined by the systematic absences in the data, was found (*e.g.* P1, P2(1), C2, and P21212). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model compatible with the proposed structure.

[0321] All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in tables below. The absolute stereochemistry was set to conform to previously studied samples of the same compound.

[0322] The single crystal X-ray crystallography data for Formula I Forms I-IV are summarized in Table 2A below. The single crystal X-ray crystallography data for Formula I Forms V-VIII are summarized in Table 2A-I below. The indexing data for Formula II Form I is summarized in Table 2C below. The single crystal X-ray crystallography data for the co-crystals of the present invention summarized in Table 2C below. The single crystal X-ray crystallography data for Formula III Forms I-III is summarized in Table 2D-I below. Data from further characterization of the crystals are summarized in Tables 3A and 3B below. Data from further characterization of the crystals are also summarized in Tables 3A-I and 3C-I below.

Table 2A: Single Crystal Data for Formula I Forms I – IV and Formula II Form I

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Form and Identification	Solvent	Solvent in lattice	Density (g/cm³)	Unit Cell Dimensions					
				Distance (Å)			Angle (°)		
				a	b	c	α	β	γ
Formula I Form I	IPAc	none	1.609	11.4498 (4)	8.4767 (3)	19.9163 (8)	90	106.286 (2)	90
Formula I Form II	IPAc	0.125 mole water	1.537	8.5226 (7)	26.934 (2)	8.6861 (8)	90	101.862 (2)	90
Formula I Form III	MIBK	none	1.537	18.002 (2)	10.9517 (12)	20.687 (2)	90	107.770 (4)	90
Formula I Form IV	methanol	0.67 mole water	1.484	20.948 (2)	16.5172 (9)	13.2051 (8)	90	108.972 (4)	90

Table 2A-I: Single Crystal Data for Formula I Forms V – VIII

Form and Identification	Solvent	Solvent in lattice	Density (g/cm^3)	Unit Cell Dimensions					
				Distance (Å)			Angle (°)		
				a	b	c	α	β	γ
Formula I Form V	water	0.5 mole water	1.573	8.4993 (6)	8.7290 (8)	13.861 9 (13)	99.27 8 (9)	101.427 (4)	100.49 4 (4)
Formula I Form VI	methanol/water	0.5 mole water 0.5 mole methanol	1.545	19.516 3 (5)	6.4593 (2)	16.606 6 (5)	90	103.5680 (13)	90
Formula I Form VII	methanol	1.08 mole water	1.468	30.785 (12)	16.685 (6)	25.956 (10)	90	108.189 (10)	90
Formula I Form VIII	methanol	None	1.560	10.324 2 (18)	10.782 6 (17)	17.848 (3)	90	105.578 (8)	90

Table 2B: Indexing Data for Formula II Form I

Form and Identification	Solvent	Unit Cell Dimensions					
		Distance (Å)			Angle (°)		
		a	b	c	α	β	γ
Formula II Form I	methanol	9.105	13.986	31.384	90	90	90

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[0323] The single crystal X-ray crystallography data for Formula II Form I is summarized in Table 2B-I below.

Table 2B-I: Single Crystal Data for Formula II, Form I

C42 H34 F6 N6 Na2 O10	Acquisition Temp.	Space Group	Z	Unit Cell Dimensions					
	100(2) K	P212121	4	Distance (Å)			Angle (°)		
Form and Identification	Solvent	Solvent in lattice	Density (Mg/m^3)	a	b	c	α	β	γ
Formula II Form I	Ethanol/DMF	none	1.614	8.9561 (10)	13.9202 (14)	31.115 (3)	90	90	90

Table 2C: Single Crystal Data for Formula I Co-Crystals

Form and Identification	Ratio Formula I: coformer	Solvent	Solvent in lattice (ratio)	Density (Mg/m^3)	Unit Cell Dimensions					
					Distance (Å)			Angle (°)		
					a	b	c	α	β	γ
Formula I Citric Acid co-crystal	1:2	THF	None	1.608	7.4315 (6)	15.575 5 (13)	15.685 6 (13)	88.78 4 (2)	77.029 (2)	76.83 2 (2)
Formula I Fumaric acid co-crystal	1:1	THF	THF (0.375 mole)	1.503	26.767 (5)	8.2313 (14)	24.089 (4)	90	99.283 (4)	90
Formula I Oxalic Acid co-crystal	1:1	THF	None	1.604	7.8562 (3)	14.503 1 (5)	19.975 6 (7)	90	101.29 1 (2)	90

Table 2D-1. Single Crystal Data for Formula III, Forms I-III

			Unit Cell Dimensions					
			Distance (Å)			Angle (°)		
Form and Identification	Solvent	Density (Mg/m^3)	a	b	c	α	β	γ
Formula III Form I	Ethanol/water	1.498	32.0409 (11)	10.2935 (4)	15.4691 (7)	90	90	90
Formula III Form II	Acetonitrile/water	1.336	32.0285 (17)	10.3029 (7)	15.5363 (10)	90	90	90
Formula III Form III	Methanol	1.483	8.8412 (3)	10.8837 (4)	13.9107 (5)	71.3620 (10)	76.343 (2)	82.943 (2)

Table 3A: Crystal Data and Structure Refinement for Formula I Forms I – IV

Property	Formula I Form I	Formula I Form II	Formula I Form III	Formula I Form IV
Empirical formula	$C_{21}H_{18}F_3N_3O_5$	$C_{21}H_{18.25}F_3N_3O_{5.12}$	$C_{21}H_{18}F_3N_3O_5$	$C_{21}H_{19.3}F_3N_3O_{5.67}$
Formula weight	449.38	451.64	449.38	461.46
Temperature	100(2) K	200(2) K	100(2) K	100(2) K
Wavelength	1.54178 Å	0.71073 Å	1.54178 Å	1.54178 Å
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	P2(1)	P2(1)	P2(1)	C 2
Volume	1855.44(12) $Å^3$	1951.3(3) $Å^3$	3884.0(8) $Å^3$	6177.3(7) $Å^3$
Z	4	4	8	12
Density (calculated)	1.609 g/cm^3	1.537 Mg/m^3	1.537g/cm^3	1.484/m^3

Table 3A-I: Crystal Data and Structure Refinement for Formula I Forms V – VIII

Property	Formula I Form V	Formula I Form VI	Formula I Form VII	Formula I Form VIII
Empirical formula	$C_{21}H_{20}F_3N_5O_{5.5}$	$C_{21.5}H_{20}F_3N_5O_6$	$C_{21}H_{18}F_{13}N_{13}O_{6.08}$	$C_{21}H_{18}F_3N_5O_5$
Formula weight	459.40	473.40	466.72	449.38
Temperature	100(2) K	200(2) K	100(2) K	100(2) K
Wavelength	0.71073 Å	1.54178 Å	0.71073 Å	0.71073 Å
Crystal system	Triclinic	Monoclinic	Monoclinic	Monoclinic
Space group	P2(1)	P2(1)	P2(1)	C 2
Volume	970.18(14) $Å^3$	2035.03(10) $Å^3$	12666(8) $Å^3$	1913.9(6) $Å^3$
Z	2	4	24	4
Density (calculated)	1.573 Mg/m^3	1.545 Mg/m^3	1.468 Mg/m^3	1.560 Mg/m^3

Table 3B: Crystal Data and Structure Refinement for Formula I Co-Crystals

Property	Formula I Citric Acid co-crystal	Formula I Fumaric Acid co-crystal	Formula I Oxalic Acid co-crystal
Empirical formula	$C_{33}H_{38}F_3N_5O_{19}$	$C_{26.50}H_{25}F_3N_5O_{9.25}$	$C_{23}H_{20}F_3N_5O_9$
Formula weight	833.63	592.49	539.42
Temperature	100(2) K	100(2) K	150(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	P1	C2	P2(1)
Volume	1721.9(2) $Å^3$	5237.9(16) $Å^3$	2231.95(14) $Å^3$
Z	2	8	4
Density (calculated)	1.608 Mg/m^3	1.503 Mg/m^3	1.604 g/cm^3

Table 3C-I: Crystal Data and Structure Refinement for Formula III Form I, Formula III Form II (Dimer), and Formula III, Form III

Property	Formula III Form I	Formula III Form II	Formula III Form III
Empirical formula	$C_{21}H_{17}F_3KN_3O_{10.5}$	$C_{42}H_{34}F_6K_2N_6O_{13.50}$	$C_{23}H_{23}F_3KN_3O_7$
Formula weight	575.47	1030.95	549.54
Temperature	100(2) K	100(2) K	100(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Orthorhombic	Orthorhombic	Triclinic
Space group	P 21 21 2	P 21 21 2	P 1
Volume	5101.9(4) Å^3	5126.8(6) Å^3	1230.86 (8) Å^3
Z	8	4	2
Density (calculated)	1.498 Mg/m^3	1.336 Mg/m^3	1.483 Mg/m^3

[0324] In certain embodiments of the invention, Formula III is hydrated. In certain embodiments, Formula III is hydrated with five to six water molecules.

[0325] Each of the references including all patents, patent applications and publications cited in the present application is incorporated herein by reference in its entirety, as if each of them is individually incorporated. Further, it would be appreciated that, in the above teaching of invention, the skilled in the art could make certain changes or modifications to the invention, and these equivalents would still be within the scope of the invention defined by the appended claims of the application. Each of the references including all patents, patent applications and publications cited in the present application is incorporated herein by reference in its entirety, as if each of them is individually incorporated. Further, it would be appreciated that, in the above teaching of invention, the skilled in the art could make certain changes or modifications to the invention, and these equivalents would still be within the scope of the invention defined by the appended claims of the application.

What is Claimed:

1. A compound selected from the group consisting of:

(2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form I;

(2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form II;

(2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form III;

(2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form IV;

(2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form V;

(2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form VI;

(2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form VII;

(2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form VIII;

(2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide fumaric acid co-crystal;

(2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide citric acid co-crystal;

(2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide oxalic acid co-crystal;

potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form II; and

potassium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form III.

2. A crystalline form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the crystalline form is Form I.

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3. The crystalline form of claim 2, characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 13.1°, 16.2°, and 20.6° 2-θ ± 0.2° 2-θ

4. The crystalline form of claim 3, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 25.0° and 27.4° 2-θ ± 0.2° 2-θ.

5. The crystalline form of claim 3 or 4, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 9.3° and 10.5° 2-θ ± 0.2° 2-θ.

6. The crystalline form of any one of claims 3 to 5, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 11.4°, 13.9°, 17.4°, and 22.3° 2-θ ± 0.2° 2-θ.

7. The crystalline form of any one of claims 3 to 6, characterized by an x-ray powder diffraction (XRPD) pattern substantially as set forth in Figure 1.

8. The crystalline form of any one of claims 3 to 7, characterized by differential scanning calorimetry (DSC) pattern substantially as set forth in Figure 7.

9. The crystalline form of any one of claims 3 to 8, characterized by a dynamic vapor sorption (DVS) pattern substantially as set forth in Figure 13.

10. A crystalline form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the crystalline form is Form II.

11. The crystalline form of claim 10, characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 6.6°, 10.6°, and 12.5° 2-θ ± 0.2° 2-θ

12. The crystalline form of claim 11, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 16.2° and 21.4° 2-θ ± 0.2° 2-θ.

13. The crystalline form of any one of claims 11 or 12, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 14.3°, 23.5°, and 25.6° 2-θ ± 0.2° 2-θ.

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14. The crystalline form of any one of claims 10 to 13, characterized by an x-ray powder diffraction (XRPD) pattern substantially as set forth in Figure 2.

15. A crystalline form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the crystalline form is Form III.

16. The crystalline form of claim 15, characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 9.6°, 14.0°, and 18.5° 2-θ ± 0.2° 2-θ

17. The crystalline form of claim 16, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 20.0° and 22.5° 2-θ ± 0.2° 2-θ.

18. The crystalline form of claim 16 or 17, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 12.1° and 16.2° 2-θ ± 0.2° 2-θ.

19. The crystalline form of any one of claims 16 to 18, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 25.0°, 27.0°, and 29.0° 2-θ ± 0.2° 2-θ.

20. The crystalline form of any one of claims 15 to 19, characterized by an x-ray powder diffraction (XRPD) pattern substantially as set forth in Figure 3.

21. The crystalline form of any one of claims 15 to 20, characterized by differential scanning calorimetry (DSC) pattern substantially as set forth in Figure 8.

22. The crystalline form of any one of claims 15 to 21, characterized by a dynamic vapor sorption (DVS) pattern substantially as set forth in Figure 14.

23. A crystalline form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the crystalline form is Form IV.

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24. The crystalline form of claim 23, characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 6.2°, 16.3°, and 22.3° 2-θ ± 0.2° 2-θ.

25. The crystalline form of claim 24, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 22.7° and 25.8° 2-θ ± 0.2° 2-θ.

26. The crystalline form of claim 24 or 25, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 8.6° and 13.2° 2-θ ± 0.2° 2-θ.

27. The crystalline form of any one of claims 24 to 26, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 18.7°, 20.0°, and 27.7° 2-θ ± 0.2° 2-θ.

28. The crystalline form of any one of claims 23 to 27, characterized by an x-ray powder diffraction (XRPD) pattern substantially as set forth in Figure 4.

29. A crystalline form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the crystalline form is Form V.

30. A crystalline form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the crystalline form is Form VI.

31. A crystalline form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the crystalline form is Form VII.

32. A crystalline form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, wherein the crystalline form is Form VIII.33. A crystalline form of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide oxalic acid co-crystal.

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33. The crystalline form of claim 32, characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 14.5°, 17.1°, and 19.1° 2-θ ± 0.2° 2-θ.

34. The crystalline form of claim 34, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 21.8° and 26.5° 2-θ ± 0.2° 2-θ.

35. The crystalline form of claim 33 or 34, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 7.6° and 9.1° 2-θ ± 0.2° 2-θ.

36. The crystalline form of any one of claims 33 to 35, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 11.6°, 29.7°, and 39.4° 2-θ ± 0.2° 2-θ.

37. The crystalline form of any one of claims 32 to 36, characterized by an x-ray powder diffraction (XRPD) pattern substantially as set forth in Figure 6.

38. A pharmaceutical composition comprising a therapeutically effective amount of the forms of any one of claims 1 to 37 and a pharmaceutically acceptable carrier or excipient.

39. The pharmaceutical composition of claim 38, further comprising one to three additional therapeutic agents.

40. The pharmaceutical composition of claim 39, wherein the additional therapeutic agents are each anti-HIV drugs.

41. The pharmaceutical composition of claim 39 or claim 40, wherein the additional therapeutic agents are each independently selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and other drugs for treating HIV.

42. The pharmaceutical composition of any one of claims 39 to 41, wherein at least two of the additional therapeutic agents are each HIV nucleotide or nucleoside inhibitors of reverse transcriptase.

43. The pharmaceutical composition of claim 38, further comprising tenofovir disoproxil fumarate and emtricitabine.

44. The pharmaceutical composition of claim 38, further comprising tenofovir alafenamide and emtricitabine.

45. The pharmaceutical composition of claim 38, further comprising tenofovir alafenamide hemifumarate and emtricitabine.

46. The pharmaceutical composition of any one of claims 38 to 45, wherein the pharmaceutical composition is in a unit dosage form.

47. The pharmaceutical composition of claim 46, wherein the unit dosage form is a tablet.

48. A pharmaceutical composition prepared by combining a therapeutically effective amount of a form of any one of claims 1 to 37 with a pharmaceutically acceptable carrier or excipient.

49. Use of a form of any one of claims 1 to 37 for treating or prophylactically preventing an HIV infection.

50. Use of a form of any one of claims 1 to 37 for the manufacture of a medicament for treating or prophylactically preventing an HIV infection.

51. A form of any one of claims 1 to 37 for use in a method for treating or prophylactically preventing an HIV infection.

52. A method for treating or prophylactically preventing an HIV infection in a human in need thereof, comprising administering to the human a therapeutically effective amount of a form of any one of claims 1 to 37.

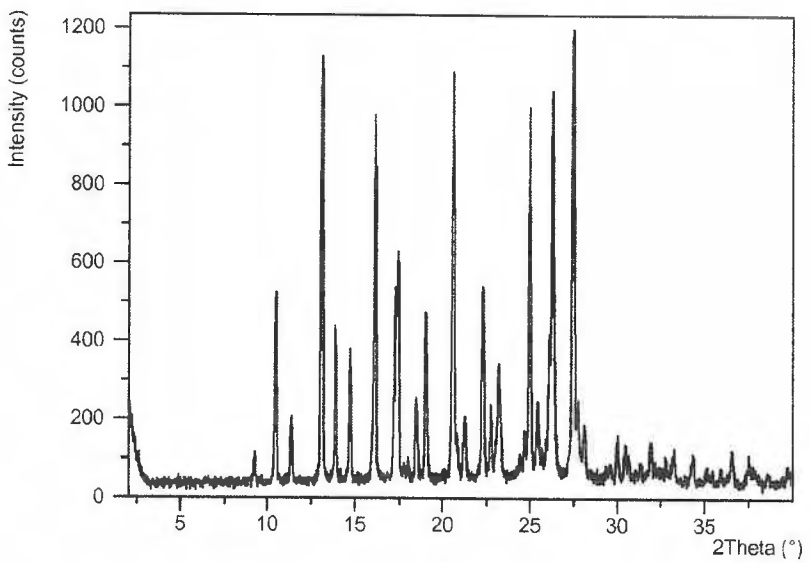


Figure 1

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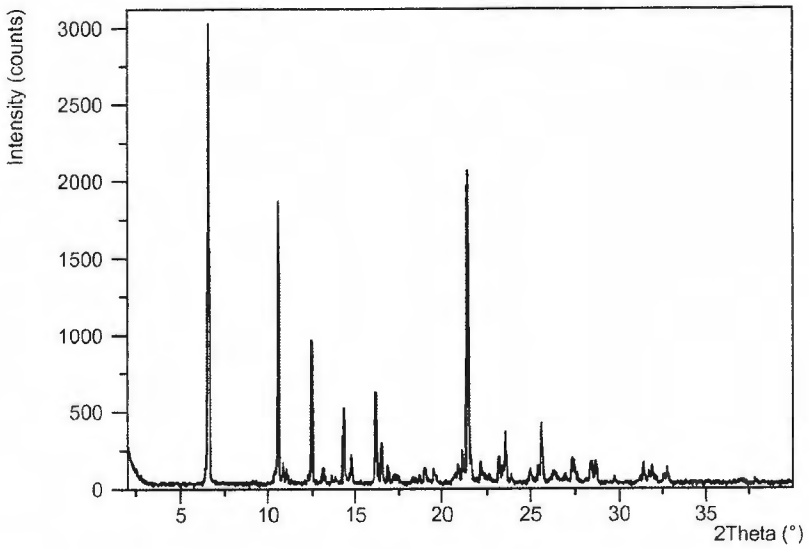


Figure 2

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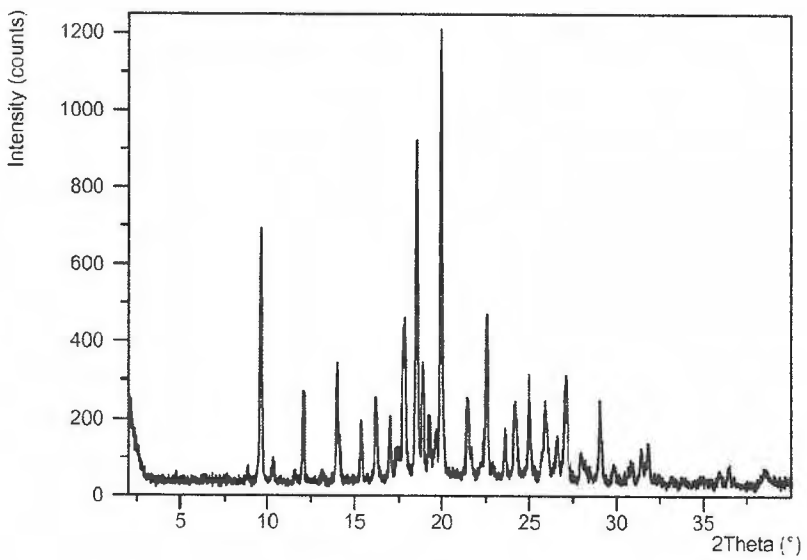


Figure 3

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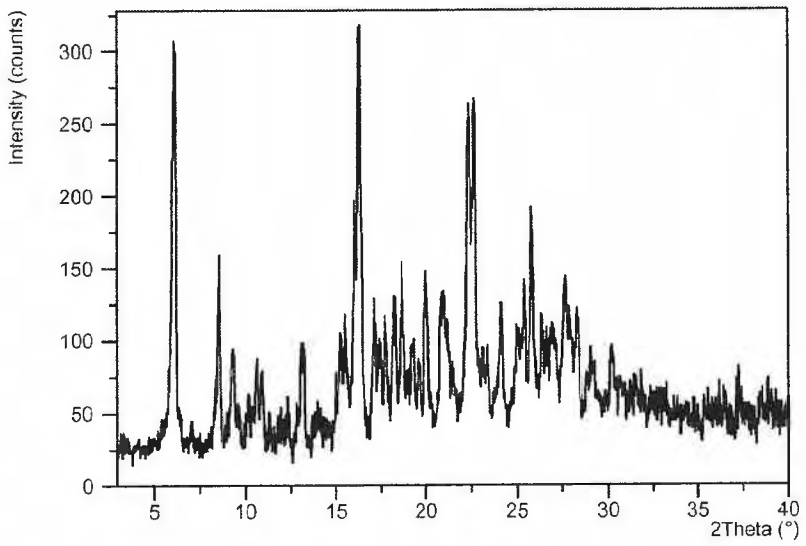


Figure 4

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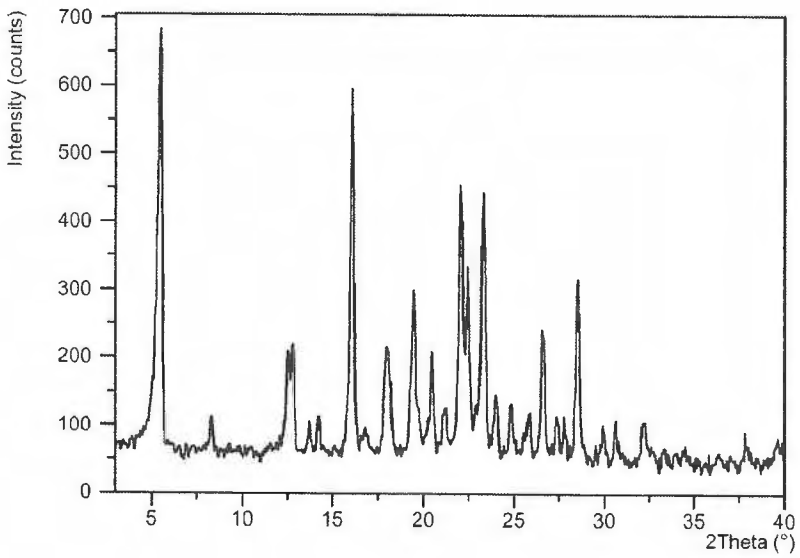


Figure 5

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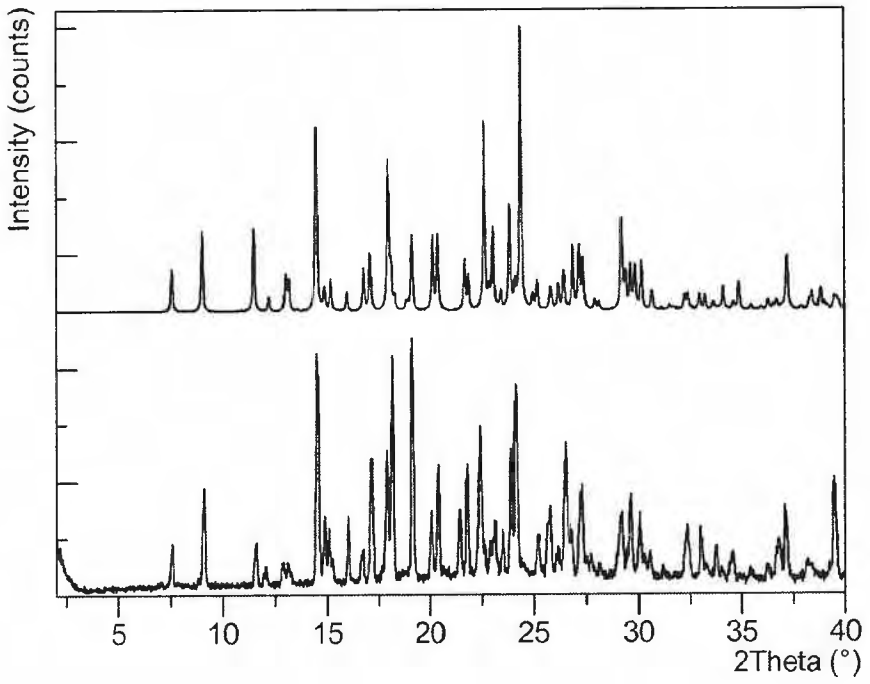


Figure 6

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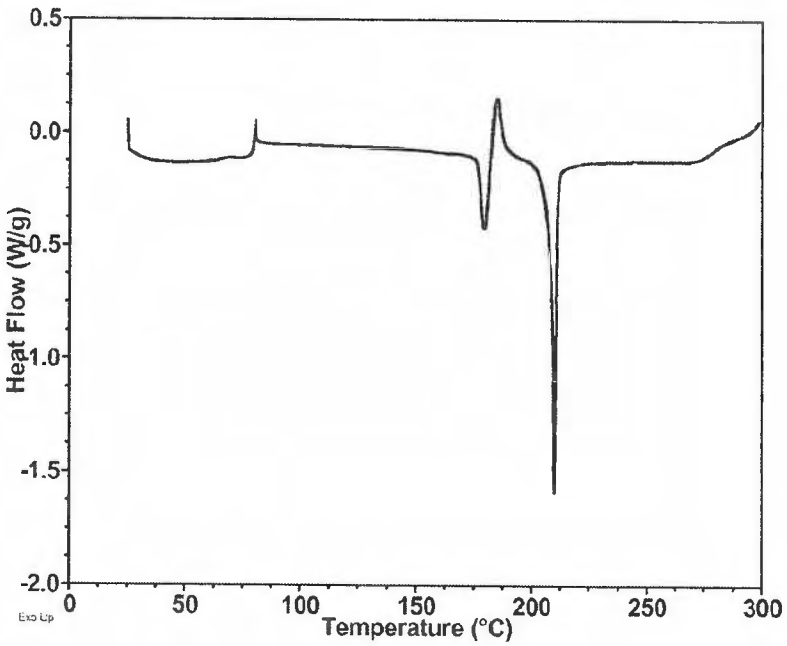


Figure 7

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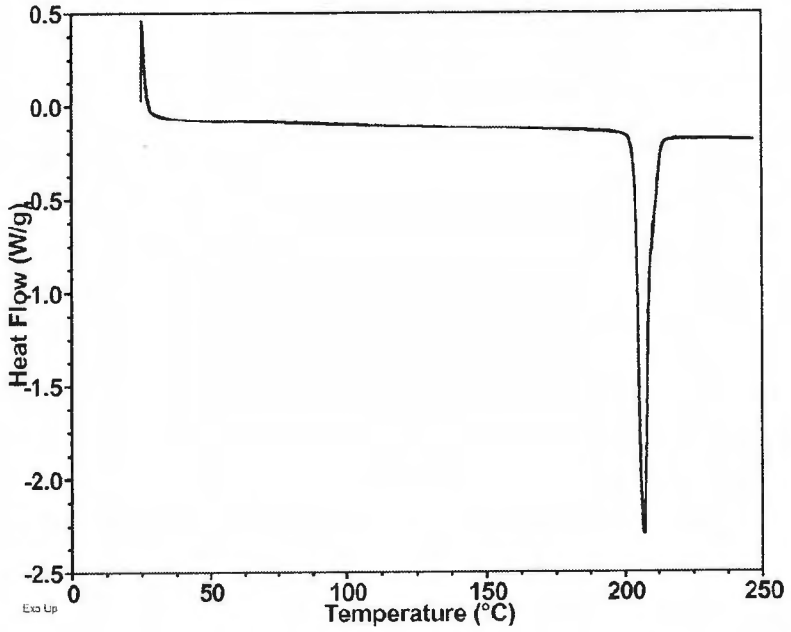


Figure 8

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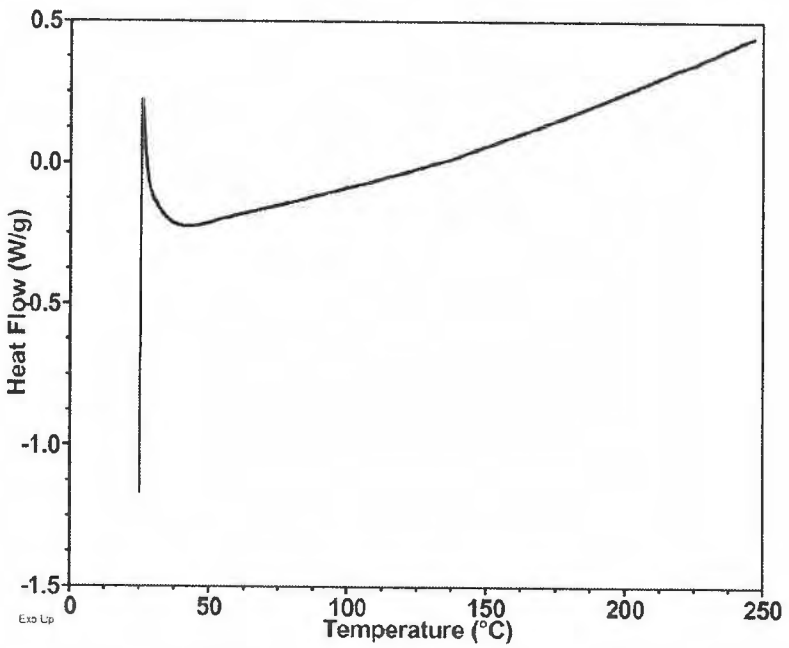


Figure 9

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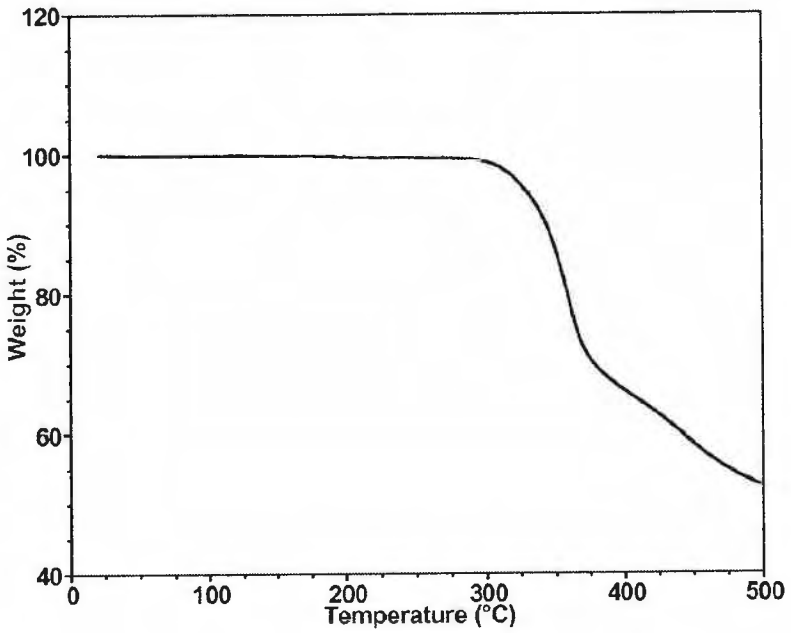


Figure 10

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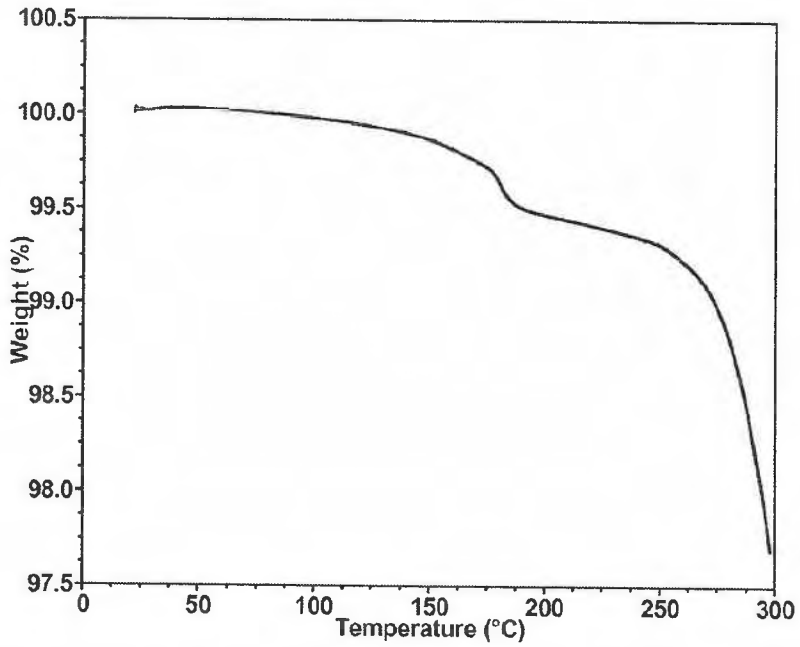


Figure 11

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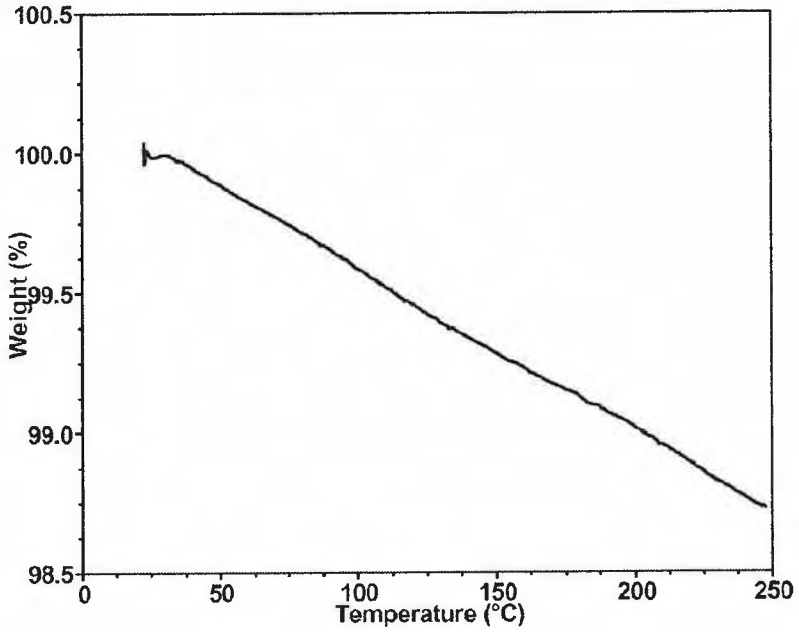


Figure 12

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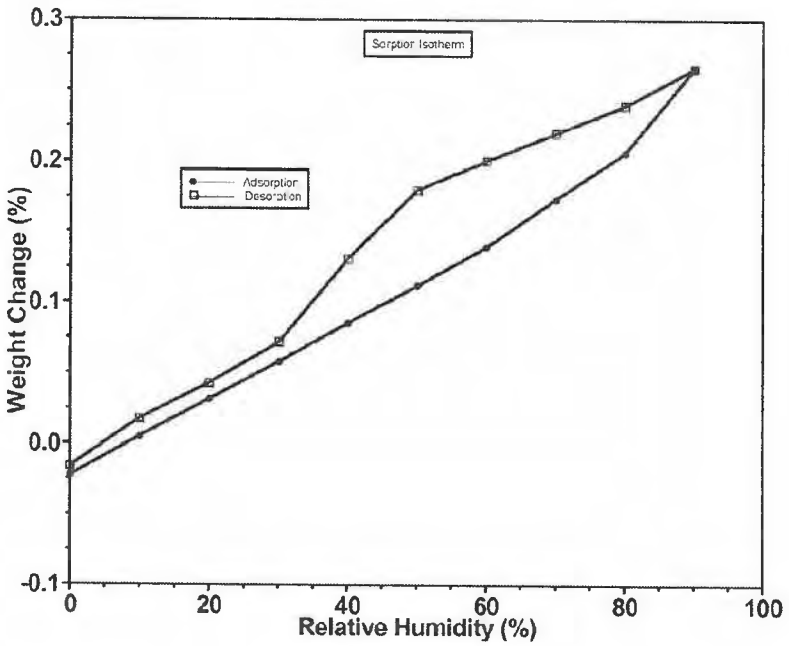


Figure 13

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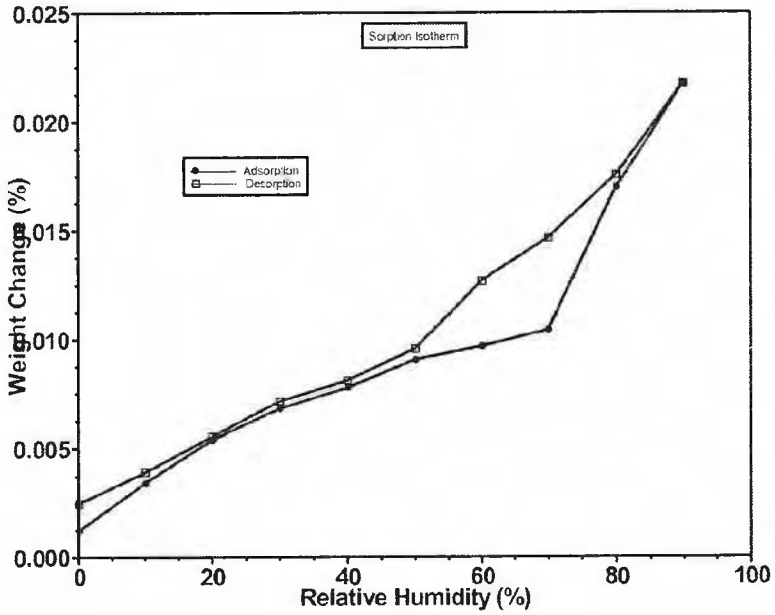


Figure 14

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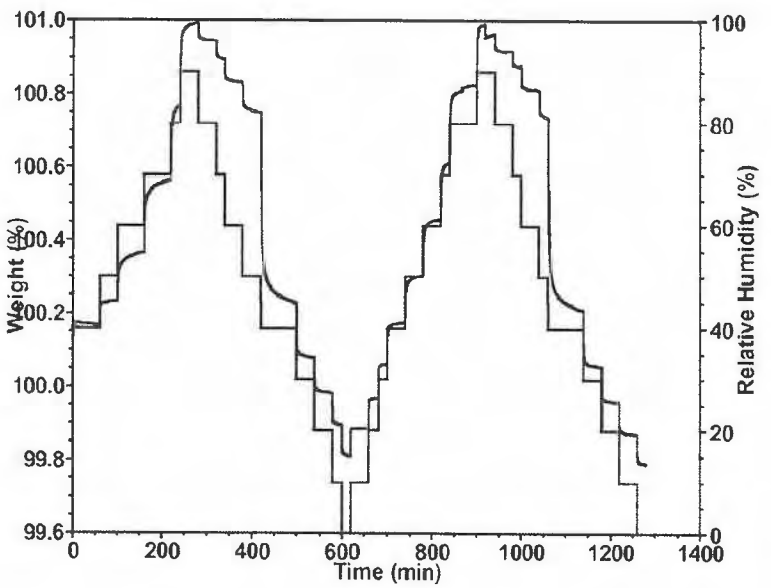


Figure 15

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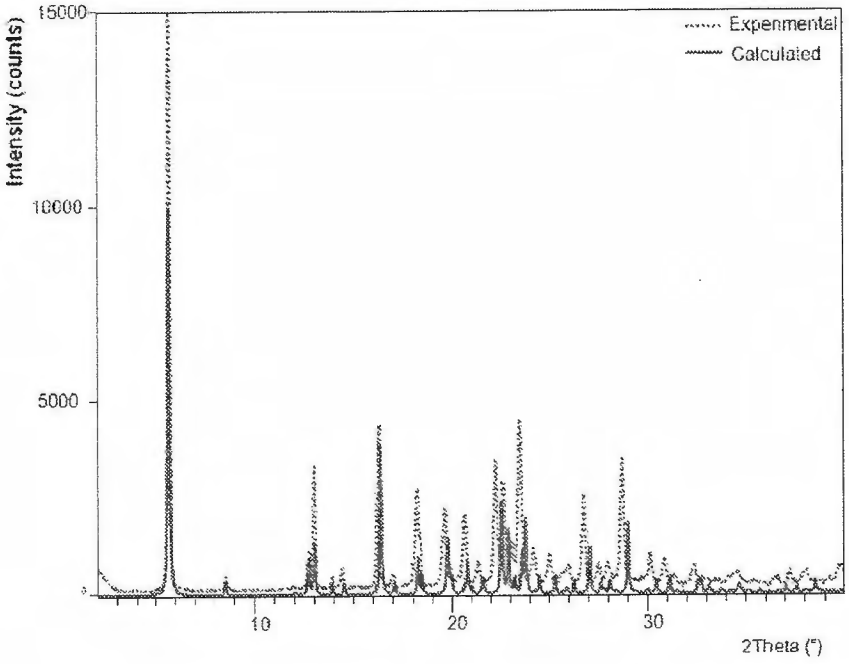


Figure 16

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/036784

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/14 A61K31/537 A61P31/18
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/116764 A1 (SHIONOGI & CO [JP]; JOHNS BRIAN ALVIN [US]; KAWASUJI TAKASHI [JP]; TAI) 2 November 2006 (2006-11-02) abstract pages 8, 46-49 pages 65, 67 compounds Z-1, Z-6, Z-10, Z-35, Z-36, Z-52 examples ZZ-19, ZZ-20 claims 1-56 ----- -/--	1-52

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 September 2015	29/09/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax (+31-70) 340-3016	Dunet, Guillaume

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1132 of 1915

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/036784

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CAIRA: "Crystalline Polymorphism of Organic Compounds", TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, January 1998 (1998-01), pages 163-208, XP008166276, ISSN: 0340-1022 pages 165-166 pages 177-180, paragraph 3.1.	1-52
X,P	WO 2014/100323 A1 (GILEAD SCIENCES INC [US]) 26 June 2014 (2014-06-26) abstract pages 99-101; example 42 claims 1-108	1-52

2

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/036784

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006116764 A1	02-11-2006	AU 2006239177 A1	02-11-2006
		BR PI0610030 A2	11-10-2011
		CA 2606282 A1	02-11-2006
		DK 1874117 T3	23-09-2013
		DK 2465580 T3	10-03-2014
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		EP 2527007 A1	28-11-2012
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		US 2014221356 A1	07-08-2014
		UY 35213 A	30-06-2014
		WO 2014100323 A1	26-06-2014

Form PCT/ISA/210 (patent family annex) (April 2005)

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(19) World Intellectual Property Organization
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WIPO | PCT

(10) International Publication Number
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A61K 31/535 (2006.01)

(21) International Application Number:
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(22) International Filing Date:
19 June 2015 (19.06.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/015,245 20 June 2014 (20.06.2014) US

(71) Applicant: **GILEAD SCIENCES, INC.** [US/US]; 333 Lakeside Drive, Foster City, CA 94404 (US).

(72) Inventors: **CARRA, Ernest, A.**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). **CHEN, Irene**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). **ZIA, Vahid**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US).

(74) Agents: **EDWARDS, Mary, J.** et al.; Gilead Sciences, Inc., 333 Lakeside Drive, Forster City, CA 94404 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

(54) Title: SODIUM (2R, 5S, 13AR) -7, 9-DIOXO-10- ((2,4,6-TRIFLUOROBENZYL) CARBAMOYL) -2, 3, 4, 5, 7, 9, 13, 13A-OCTAHYDRO-2, 5-METHANOPYRIDO [1',2' : 4.5] PYRAZINO [2, 1-B] OXAZEPIN-8-OLATE

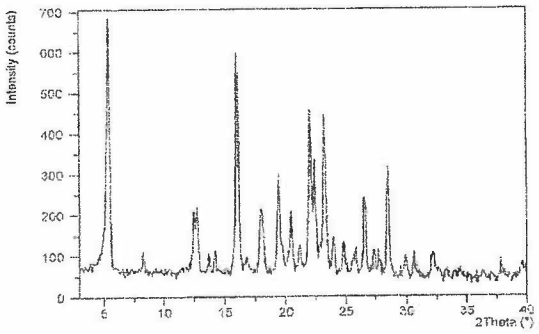


Figure 1

(57) Abstract: The present Invention relates to sodium (2R,5S,13aR)-7,9-dioxo-10 -((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5] pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

WO 2015/196116 A1

SODIUM (2R,5S,13AR)-7,9-DIOXO-10-((2,4,6-TRIFLUOROBENZYL)CARBAMOYL)-2,3,4,5,7,9,13,13A-OCTAHYDRO-2,5-METHANOPYRIDO[1',2':4,5]PYRAZINO[2,1-B][1,3]OXAZEPIN-8-OLATE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit under 35 U.S.C. 119(e) of U.S. Provisional Patent Application Serial No. 62/015,245, filed June 20, 2014, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD

[0002] The present invention relates to sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, the crystalline forms, the pharmaceutical formulations, and the therapeutic uses thereof.

BACKGROUND

[0003] Human immunodeficiency virus infection and related diseases are a major public health problem worldwide. Human immunodeficiency virus type 1 (HIV-1) encodes three enzymes which are required for viral replication: reverse transcriptase, protease, and integrase. Although drugs targeting reverse transcriptase and protease are in wide use and have shown effectiveness, particularly when employed in combination, toxicity and development of resistant strains have limited their usefulness (Palella, et al. *N. Engl. J Med.* (1998) 338:853–860; Richman, D. D. *Nature* (2001) 410:995–1001).

[0004] A goal of antiretroviral therapy is to achieve viral suppression in the HIV infected patient. Treatment guidelines published by the United States Department of Health and Human Services provide that achievement of viral suppression requires the use of combination therapies, i.e., several drugs from at least two or more drug classes. In addition, decisions regarding the treatment of HIV infected patients are complicated when the patient requires treatment for other medical conditions. Because the standard of care requires the use of multiple different drugs to suppress HIV, as well as to treat other conditions the patient may be experiencing, the potential for drug interaction is a criterion for selection of a drug regimen. As such, there is a need for antiretroviral therapies having a decreased potential for

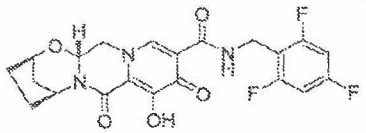
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drug interactions.

[0005] As discussed in co-pending application United States Serial No. 14/133,855, filed December 19, 2013 entitled "POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE", (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide demonstrates anti-viral activity. As discussed in co-pending application PCT Serial No. US2013/076367, filed December 19, 2013 entitled "POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE", (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide demonstrates anti-viral activity.

[0006] (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, (Formula I), has the following structure:

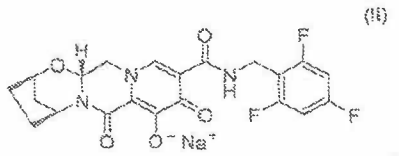
(I)



[0007] It is desired to have physically stable forms of the compound that are suitable for the therapeutic use and the manufacturing process.

BRIEF SUMMARY

[0008] In certain embodiments, the present invention is directed to sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, having the following structure (Formula II):



(II)

[0009] In a still further embodiment, the present invention is directed to crystalline sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0010] In a still further embodiment, the present invention is directed to sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0011] In a certain embodiment, the present invention is directed to pharmaceutical formulations comprising sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0012] In another embodiment, the present invention is directed to methods of treating or prophylactically preventing an HIV infection by administering sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0013] In another embodiment, the present invention is directed to sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate for use in methods of treating or prophylactically preventing an HIV infection.

[0014] In another embodiment, the present invention is directed to the use of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate in the manufacture of a medicament for treating or prophylactically preventing an HIV infection.

DESCRIPTION OF THE FIGURES

[0015] **Figure 1:** XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-

trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0016] **Figure 2:** DSC for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0017] **Figure 3:** TGA for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0018] **Figure 4:** DVS for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0019] **Figure 5:** Dissolution profiles of Formula I Form I, Formula I Form III, and Formula II Form I.

[0020] **Figure 6:** Solubility profiles of Formula I Form III and Formula II Form I in Fasted-State Simulated Gastric Fluid (FaSSGF).

[0021] **Figure 7:** Solubility profiles of Formula I Form III and Formula II Form I in Fed-State Simulated Intestinal Fluid (FeSSIF) and Fasted-State Simulated Intestinal Fluid (FaSSIF).

[0022] **Figure 8:** Calculated and Experimental XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

DETAILED DESCRIPTION

[0023] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the invention. However, one skilled in the art will understand that the invention may be practiced without these details. The description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the claimed subject matter, and is not intended to limit the appended claims to the specific embodiments illustrated. The

headings used throughout this disclosure are provided for convenience only and are not to be construed to limit the claims in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

Definitions

[0024] Unless the context requires otherwise, throughout the present specification and claims, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is as "including, but not limited to".

[0025] Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

[0026] The invention disclosed herein is also meant to encompass all pharmaceutically acceptable compounds of Formulas (I) and (II) being isotopically-labeled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. These radiolabeled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action, or binding affinity to pharmacologically important site of action. Certain isotopically-labeled compounds of Formulas (I) and (II), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[0027] Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability. For example, *in vivo* half-life may increase or dosage requirements may be reduced. Thus, heavier isotopes may be preferred in some circumstances.

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[0028] Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of Formulas (I) and (II) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0029] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0030] "Optional" or "optionally" means that the subsequently described event or circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

[0031] "Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[0032] A "pharmaceutical composition" refers to a formulation of a compound of the invention and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, *e.g.*, humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.

[0033] "Effective amount" or "therapeutically effective amount" refers to an amount of a compound according to the invention, which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. Such an amount would be sufficient to elicit the biological or medical response of a tissue system, or patient that is sought by a researcher or clinician. The amount of a compound according to the invention which constitutes a therapeutically effective amount will vary depending on such factors as the compound and its biological activity, the composition used for administration, the time of administration, the route of

administration, the rate of excretion of the compound, the duration of the treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination with or coincidentally with the compounds of the invention, and the age, body weight, general health, sex and diet of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.

[0034] The term "treatment" as used herein is intended to mean the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of HIV infection and/or to reduce viral load in a patient. The term "treatment" also encompasses the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood, and the administration of a compound or composition according to the present invention to prevent perinatal transmission of HIV from mother to baby, by administration to the mother before giving birth and to the child within the first days of life. In certain embodiments, the term "treatment" as used herein is intended to mean the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of HIV infection and/or to reduce viral load in a patient. In certain embodiments, the term "treatment" as used herein is further or alternatively intended to mean the administration of a compound or composition according to the present invention to maintain a reduced viral load in a patient. The term "treatment" also encompasses the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease; and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood, and the administration of a compound or composition according to the present invention to prevent perinatal transmission of HIV from mother to baby, by administration to the mother before giving birth and to the child within the first days of life. In certain embodiments, the term "treatment" as used herein is further or alternatively intended to mean the administration of a compound or composition according to the present invention post-exposure of the individual to the virus as a subsequent or additional therapy to a first-line therapy (e.g., for maintenance of low viral load).

[0035] "Prevention" or "preventing" means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. The term "prevention" also encompasses the administration of a compound or composition according to the present invention pre-exposure of the individual to the virus (e.g., pre-exposure prophylaxis), to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood.

[0036] The terms "Subject" or "patient" refer to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation or experiment. The methods described herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal (or the patient). In some embodiments the subject (or the patient) is human, domestic animals (e.g., dogs and cats), farm animals (e.g., cattle, horses, sheep, goats and pigs), and/or laboratory animals (e.g., mice, rats, hamsters, guinea pigs, pigs, rabbits, dogs, and monkeys). In one embodiment, the subject (or the patient) is a human. "Human (or patient) in need thereof" refers to a human who may have or is suspect to have diseases or conditions that would benefit from certain treatment; for example, being treated with the compounds disclosed herein according to the present application.

[0037] The term "antiviral agent" as used herein is intended to mean an agent (compound or biological) that is effective to inhibit the formation and/or replication of a virus in a human being, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a human being.

[0038] The term "inhibitor of HIV replication" as used herein is intended to mean an agent capable of reducing or eliminating the ability of HIV to replicate in a host cell, whether *in vitro, ex vivo* or *in vivo*.

[0039] A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present invention includes tautomers of any said compounds.

[0040] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X". Also, the singular forms "a" and "the" include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to "the compound" includes a plurality of such compounds and reference to "the assay"

includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[0041] "Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0042] "Unit dosage forms" are physically discrete units suitable as unitary dosages for subjects (*e.g.*, human subjects and other mammals), each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

Crystalline Form

Formula II

[0043] It is desirable to develop a crystalline form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate that may be useful in the synthesis of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. A form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate may be an intermediate to the synthesis of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. A form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate may be the final product in the synthesis of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. A polymorphic form or polymorph or cocrystal may have properties such as bioavailability and stability at certain conditions that may be suitable for medical or pharmaceutical uses.

[0044] A crystalline form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-

trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate may provide the advantage of bioavailability and stability, suitable for use as an active ingredient in a pharmaceutical composition. In certain embodiments, a crystalline form sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate provides an advantage of improved bioavailability (Table 3) and/or stability (Table 4). Variations in the crystal structure of a pharmaceutical drug substance or active ingredient may affect the dissolution rate (which may affect bioavailability, *etc.*), manufacturability (*e.g.*, ease of handling, ability to consistently prepare doses of known strength) and stability (*e.g.*, thermal stability, shelf life, etc.) of a pharmaceutical drug product or active ingredient. Such variations may affect the preparation or formulation of pharmaceutical compositions in different dosage or delivery forms, such as solid oral dosage form including tablets and capsules. Compared to other forms such as non-crystalline or amorphous forms, crystalline forms may provide desired or suitable hygroscopicity, particle size controls, dissolution rate, solubility, purity, physical and chemical stability, manufacturability, yield, and/or process control. Thus, crystalline forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate may provide advantages such as: improving the manufacturing process of an active agent or the stability or storability of a drug product form of the compound or an active ingredient, and/or having suitable bioavailability and/or stability as an active agent.

[0045] The use of certain solvents has been found to produce different polymorphic forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, including polymorphic Form I, which may exhibit one or more favorable characteristics described above. In certain embodiments, Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate provides an advantage of improved bioavailability (Table 3) and/or stability (Table 4). The processes for the preparation of the polymorphs described herein and characterization of these polymorphs are described in greater detail below.

[0046] The compound name provided above is named using ChemBioDraw Ultra and

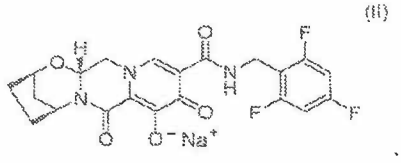
one skilled in the art understands that the compound structure may be named or identified using other commonly recognized nomenclature systems and symbols. By way of example, the compound may be named or identified with common names, systematic or non-systematic names. The nomenclature systems and symbols that are commonly recognized in the art of chemistry including but not limited to Chemical Abstract Service (CAS) and International Union of Pure and Applied Chemistry (IUPAC). Accordingly, the compound structure provided above may be named or identified as sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate under IUPAC.

[0047] In particular embodiments, crystalline forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate are disclosed.

Formula II, Form I

[0048] In a certain embodiment, novel forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, having the following structure (Formula II) are disclosed:

(II)



[0049] In a further embodiment, crystalline forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate are disclosed.

[0050] In a certain embodiment, sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is disclosed.

[0051] In one embodiment, provided is polymorphic Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-

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methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the polymorph exhibits an X-ray powder diffraction (XRPD) pattern substantially as shown in FIG. 1 and/or FIG. 8. Polymorphic sodium Form I may exhibit a differential scanning calorimetry (DSC) thermogram substantially as shown in FIG. 2. Polymorphic sodium Form I may exhibit a thermographic analysis (TGA) graph substantially as shown in FIG. 3. Polymorphic sodium Form I may exhibit dynamic vapour sorption (DVS) graphs substantially as shown in FIG. 4.

[0052] The term "substantially as shown in" when referring, for example, to an XRPD pattern, a DSC thermogram, or a TGA graph includes a pattern, thermogram or graph that is not necessarily identical to those depicted herein, but that falls within the limits of experimental error or deviations when considered by one of ordinary skill in the art.

[0053] Polymorphic sodium Form I may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 8.9561 (10) Å; b = 13.9202 (14) Å; c = 31.115 (3) Å; α = 90 °; β = 90 °; and γ = 90 °.

[0054] In some embodiments of polymorphic sodium Form I, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or all of the following (a)-(j) apply: (a) polymorphic Form I has an XRPD pattern substantially as shown in FIG. 1 and/or FIG. 8; (b) polymorphic sodium Form I has a DSC thermogram substantially as shown in FIG. 2; (c) polymorphic sodium Form I has a TGA graph substantially as shown in FIG. 3; (d) polymorphic sodium Form I has DVS graphs substantially as shown in FIG. 4; (e) polymorphic sodium Form I has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 8.9561 (10) Å; b = 13.9202 (14) Å; c = 31.115 (3) Å; α = 90 °; β = 90 °; and γ = 90 °; (f) polymorphic sodium Form I has an orthorhombic crystal system; (g) polymorphic sodium Form I has a P212121 space group; (h) polymorphic sodium Form I has a volume of 3879.2(7) $Å^3$; (i) polymorphic Form I has a Z value of 4; and (j) polymorphic Form I has a density of 1.614 Mg/m^3.

[0055] In some embodiments, polymorphic sodium Form I has at least one, at least two, at least three, at least four, or all of the following properties:

a. an XRPD pattern substantially as shown in FIG. 1 and/or FIG. 8;

b. a DSC thermogram substantially as shown in FIG. 2;

c. TGA graphs substantially as shown in FIG. 3;

d. DVS graphs substantially as shown in FIG. 4; and

e. a unit cell, as determined by crystal X-ray crystallography, of the following dimensions a = 8.9561 (10) Å; b = 13.9202 (14) Å; c = 31.115 (3) Å; α = 90 °; β = 90 °; and γ = 90 °;

[0056] In some embodiments, polymorphic sodium Form I has an XRPD pattern displaying at least two, at least three, at least four, at least five, or at least six of the degree 2θ-reflections with the greatest intensity as the XRPD pattern substantially as shown in FIG. 1 and/or FIG. 8.

[0057] In certain embodiments, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, and 23.3. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, and 23.3 and one or more of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.1, 28.5, and 22.5. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, and 23.3 and one of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.1, 28.5, and 22.5. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, and 23.3 and two of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.1, 28.5, and 22.5. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, and 23.3 and three of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.1, 28.5, and 22.5. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, 23.3, 22.1, 28.5, and 22.5. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, 23.3, 22.1, 28.5, 22.5, 19.5, and 26.6. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising any three degree 2θ-reflections (+/- 0.2 degrees 2θ) selected from the group consisting of 5.5, 16.1, 23.3, 22.1, 28.5, 22.5, 19.5, 26.6, and 17.9.

Pharmaceutical Compositions

[0058] For the purposes of administration, in certain embodiments, the compounds described herein are administered as a raw chemical or are formulated as pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a compound of Formula (II), including forms and co-crystals thereof, and a pharmaceutically acceptable carrier, diluent or excipient. The compound of Formula (II) is present in the composition in an amount which is effective to treat a particular disease or condition of interest. The activity of compounds of Formula (II) can be determined by one skilled in the art, for example, as described in co-pending application Serial No. 14/133,855, filed December 19, 2013 entitled "POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE". The activity of compounds of Formula (II) can also be determined by one skilled on the art, for example, as described in co-pending PCT Serial No. US2013/076367, filed December 19, 2013 entitled, "POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE." Appropriate concentrations and dosages can be readily determined by one skilled in the art. In certain embodiments, a compound of Formula (II) is present in the pharmaceutical composition in an amount from about 25 mg to about 500 mg. In certain embodiments, a compound of Formula (II) is present in the pharmaceutical composition in an amount of about 100 mg to about 300 mg. In certain embodiments, a compound of Formula (II) is present in the pharmaceutical composition in an amount of about 5 mg to about 100 mg. In certain embodiments, a compound of Formula (II) is present in the pharmaceutical composition in an amount of about 25 mg to about 100 mg. In certain embodiments, a compound of Formula (II) is present in the pharmaceutical composition in an amount of about 50 mg to about 100 mg. In certain embodiments, a compound of Formula (II) is present in the pharmaceutical composition in an amount of about 5 mg to about 100 mg. In certain embodiments, a compound of Formula (II) is present in the pharmaceutical composition in an amount of about 5 mg, 25 mg, 50 mg, 75, mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg.

Formula II

[0059] Provided are also compositions comprising at least one polymorph (e.g., any one or more of Formula II polymorphic Forms I) as described herein. In a particular embodiment, a composition comprising Formula II polymorphic Form I, described herein is

provided. In other embodiments, the compositions described herein may comprise substantially pure polymorphic forms, or may be substantially free of other polymorphs and/or impurities.

[0060] In some embodiments, the composition comprises a polymorphic form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments are provided compositions comprising a polymorphic form as described herein, wherein the sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate within the composition is substantially pure (*i.e.*, substantially pure Form I). In particular embodiments of compositions comprising a polymorphic form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate present in the composition is Formula II, Form I, disclosed herein. In certain embodiments, the composition includes at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% of Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0061] In other embodiments of compositions comprising a polymorphic form disclosed herein, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1% of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate present in the composition are other polymorphs of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate and/or impurities.

[0062] In yet other embodiments of compositions comprising the polymorphic forms disclosed herein, impurities make up less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1% of the total mass relative to the mass of the polymorphic forms present. Impurities may, for example, include by-products from synthesizing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, contaminants, degradation products, other polymorphic forms, amorphous form, water, and solvents. In certain embodiments, impurities include by-products from the process of synthesizing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments, impurities include contaminants from the process of synthesizing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments, impurities include degradation products of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments, impurities include other polymorphic forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments, impurities include water or solvent. In certain embodiments of compositions comprising a polymorphic form disclosed herein, impurities are selected from the group consisting of by-products from synthesizing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, contaminants, degradation products, other polymorphic forms, water, solvents and combinations thereof.

[0063] In yet other embodiments, the composition comprising Formula II, Form I disclosed herein has less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about 1% by weight of amorphous or non-crystalline sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0064] In some embodiments, the term "substantially pure" or "substantially free" with respect to a particular polymorphic form of a compound means that the composition

comprising the polymorphic form contains less than 95%, less than 90%, less than 80%, less than 70%, less than 65%, less than 60%, less than 55%, less than 50%, less than 40%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, or less than 1% by weight of other substances, including other polymorphic forms and/or impurities. In certain embodiments, "substantially pure" or "substantially free of" refers to a substance free of other substances, including other polymorphic forms and/or impurities. Impurities may, for example, include by-products or left over reagents from chemical reactions, contaminants, degradation products, other polymorphic forms, water, and solvents.

Administration

[0065] Administration of the compounds disclosed herein in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration of agents for serving similar utilities. The pharmaceutical compositions described herein can be prepared by combining a compound disclosed herein with an appropriate pharmaceutically acceptable carrier, diluent or excipient, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. The pharmaceutical compositions of the invention can be prepared by combining a compound of the invention with an appropriate pharmaceutically acceptable carrier, diluent or excipient, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as solid dispersions and solid solutions. Typical routes of administering such pharmaceutical compositions include, without limitation, oral, topical, transdermal, inhalation, parenteral, sublingual, buccal, rectal, vaginal, and intranasal. In one embodiment, the pharmaceutical compositions is prepared for oral administration. In a specific embodiment, the pharmaceutical compositions is a tablet. Pharmaceutical compositions of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient. Compositions that will be administered to a subject or patient take the form of one or more dosage units, where for example, a tablet may be a single dosage unit, and a container of a compound of the invention in aerosol form may hold a plurality of dosage units. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*, 20th Edition (Philadelphia College of Pharmacy and Science, 2000). The composition to be administered will, in any

event, contain a therapeutically effective amount of a compound of the invention for treatment of a disease or condition of interest in accordance with the teachings of this disclosure.

[0066] The pharmaceutical compositions disclosed herein may be prepared by methodology well known in the pharmaceutical art. For example, a pharmaceutical composition intended to be administered by injection can be prepared by combining a compound of the invention with sterile, distilled water so as to form a solution. A surfactant may be added to facilitate the formation of a homogeneous solution or suspension. Surfactants are compounds that non-covalently interact with the compound of the invention so as to facilitate dissolution or homogeneous suspension of the compound in the aqueous delivery system.

[0067] For example, a solid pharmaceutical composition intended for oral administration can be prepared by mixing a compound of the invention with at least one suitable pharmaceutical excipient to form a solid preformulation composition, which then may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. Accordingly, in one embodiment, a pharmaceutical composition is provided, which includes a compound of Formula (II) and a pharmaceutical excipient.

[0068] The compounds disclosed herein are administered in a therapeutically effective amount, which will vary depending upon a variety of factors including the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disorder or condition; and the subject undergoing therapy. In some embodiments, the compounds of the invention can be administered alone or in combination with other antiviral agents once or twice daily for as long as the patient is infected, latently infected, or to prevent infection (e.g. for multiple years, months, weeks, or days).

Combination Therapy

[0069] In one embodiment, a method for treating or preventing an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein in combination with a therapeutically effective amount of one or more (e.g., one, two, three, one or two, or

one to three) additional therapeutic agents. In one embodiment, a method for treating an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein in combination with a therapeutically effective amount of one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents.

[0070] In one embodiment, a method for treating an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound or composition disclosed herein in combination with a therapeutically effective amount of one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents.

[0071] In certain embodiments, the present invention provides a method for treating an HIV infection, comprising administering to a patient in need thereof a therapeutically effective amount of a compound or composition disclosed herein in combination with a therapeutically effective amount of one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0072] One embodiment provides a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents for use in a method for treating or preventing an HIV infection in a human having or at risk of having the infection. One embodiment provides a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents for use in a method for treating an HIV infection in a human having or at risk of having the infection. One embodiment provides a compound disclosed herein for use in a method for treating or preventing an HIV infection in a human having or at risk of having the infection, wherein the compound is administered in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents. One embodiment provides a compound disclosed herein for use in a method for treating an HIV infection in a human having or at risk of having the infection, wherein the compound is administered in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents. In certain embodiments, the present invention provides a compound disclosed herein in combination with one or more additional therapeutic agents which are suitable for treating an HIV infection, for use in a method for treating an HIV infection. In certain embodiments, the present invention provides a compound disclosed herein for use in a

method for treating an HIV infection, wherein the compound is administered in combination with one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0073] One embodiment provides the use of a compound disclosed herein thereof, in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents in the manufacture of a medicament for treating or preventing an HIV infection in a human having or at risk of having the infection. One embodiment provides the use of a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents in the manufacture of a medicament for treating an HIV infection in a human having or at risk of having the infection. One embodiment provides the use of a compound disclosed herein in the manufacture of a medicament for treating or preventing an HIV infection in a human having or at risk of having the infection, wherein the compound is administered in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents. One embodiment provides the use of a compound disclosed herein thereof, in the manufacture of a medicament for treating an HIV infection in a human having or at risk of having the infection, wherein the compound is administered in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents. In certain embodiments, the present invention provides the use of a compound disclosed herein thereof, in combination with one or more additional therapeutic agents which are suitable for treating an HIV infection, in treating an HIV infection. In certain embodiments, the present invention provides the use of a compound disclosed herein thereof for treating an HIV infection, wherein the compound is administered in combination with one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0074] A compound as disclosed herein (e.g., any compound of Formula (II)) may be combined with one or more additional therapeutic agents in any dosage amount of the compound of Formula II (e.g., from 50 mg to 1000 mg of compound).

[0075] In one embodiment, pharmaceutical compositions comprising a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent or excipient are provided.

[0076] In one embodiment, combination pharmaceutical agents comprising a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents are provided.

[0077] In one embodiment, kits comprising a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents are provided.

[0078] In the above embodiments, the additional therapeutic agent may be an anti-HIV agent. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, entry inhibitors (e.g., CCR5 inhibitors, gp41 inhibitors (i.e., fusion inhibitors) and CD4 attachment inhibitors), CXCR4 inhibitors, gp120 inhibitors, G6PD and NADH-oxidase inhibitors, compounds that target the HIV capsid ("capsid inhibitors"; e.g., capsid polymerization inhibitors or capsid disrupting compounds such as those disclosed in WO 2013/006738 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), and WO 2013/006792 (Pharma Resources), pharmacokinetic enhancers, and other drugs for treating HIV, and combinations thereof.

[0079] In other embodiments, the additional therapeutic agent may be an anti-HIV agent. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors (e.g., CCR5 inhibitors, gp41 inhibitors (i.e., fusion inhibitors) and CD4 attachment inhibitors), CXCR4 inhibitors, gp120 inhibitors, G6PD and NADH-oxidase inhibitors, HIV vaccines, HIV maturation inhibitors, latency reversing agents (e.g., histone deacetylase inhibitors, proteasome inhibitors, protein kinase C (PKC) activators, and BRD4 inhibitors), compounds that target the HIV capsid ("capsid inhibitors"; e.g., capsid polymerization inhibitors or capsid disrupting compounds, HIV nucleocapsid p7 (NCp7) inhibitors, HIV p24 capsid protein inhibitors), pharmacokinetic enhancers, immune-based therapies (e.g., Pd-1 modulators, Pd-L1 modulators, toll like receptors modulators,, IL-15 agonists,), HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins

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(e.g., DARTs®, Duobodies®, Bites®, XmAbs®, TandAbs ®, Fab derivatives) including those targeting HIV gp120 or gp41, combination drugs for HIV, HIV p17 matrix protein inhibitors, IL-13 antagonists, Peptidyl-prolyl cis-trans isomerase A modulators, Protein disulfide isomerase inhibitors, Complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, Integrin antagonists, Nucleoprotein inhibitors, Splicing factor modulators, COMM domain containing protein 1 modulators, HIV Ribonuclease H inhibitors, Retrocyclin modulators, CDK-9 inhibitors, Dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, Ubiquitin ligase inhibitors, Deoxycytidine kinase inhibitors, Cyclin dependent kinase inhibitors Proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, HIV gene therapy, PI3K inhibitors, compounds such as those disclosed in WO 2013/006738 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), WO 2013/091096A1 (Boehringer Ingelheim), WO 2009/062285 (Boehringer Ingelheim), US20140221380 (Japan Tobacco), US20140221378 (Japan Tobacco), WO 2010/130034 (Boehringer Ingelheim), WO 2013/159064 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO2012/003497 (Gilead Sciences), WO2014/100323 (Gilead Sciences), WO2012/145728 (Gilead Sciences), WO2013/159064 (Gilead Sciences) and WO 2012/003498 (Gilead Sciences) and WO 2013/006792 (Pharma Resources), and other drugs for treating HIV, and combinations thereof.

[0080] In certain embodiments, the additional therapeutic is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof.

[0081] In certain embodiments a compound of Formula (II) is formulated as a tablet, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the tablet can contain another active ingredient for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse

transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof. In certain embodiments, the tablet can contain one or more active ingredients for treating HIV, such as HIV nucleoside or nucleotide inhibitors of reverse transcriptase. In certain embodiments, such tablets are suitable for once daily dosing.

[0082] In further embodiments, the additional therapeutic agent is selected from one or more of:

(1) HIV protease inhibitors selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;

(2) HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase selected from the group consisting of capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, TMC-120, rilpivirine, BILR 355 BS, VRX 840773, lersivirine (UK-453061), RDEA806, KM023 and MK-1439;

(3) HIV nucleoside or nucleotide inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, abacavir sulfate, amdoxovir, elvucitabine, alovudine, MIV-210, ß-FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), KP-1461, GS-9131 (Gilead Sciences), fosalvudine tidoxil (formerly HDP 99.0003), tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir alafenamide hemifumarate, tenofovir alafenamide fumarate (Gilead Sciences), GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxil, CMX-001 (Chimerix) and CMX-157 (Chimerix);

(4) HIV integrase inhibitors selected from the group consisting of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin,

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derivatives of quercetin, S-1360, AR-177, L-870812, and L-870810, raltegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, BA 011, elvitegravir, dolutegravir, dolutegravir sodium, and GSK-744;

(6) HIV non-catalytic site, or allosteric, integrase inhibitors (NCINI) including, but not limited to, BI-224436, CX0516, CX05045, CX14442, compounds disclosed in WO 2009/062285 (Boehringer Ingelheim), WO 2010/130034 (Boehringer Ingelheim), WO 2013/159064 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO 2012/003497 (Gilead Sciences), WO 2012/003498 (Gilead Sciences) each of which is incorporated by references in its entirety herein;

(7) gp41 inhibitors selected from the group consisting of enfuvirtide, sifuvirtide, albuvirtide, FB006M, and TRI-1144;

(8) the CXCR4 inhibitor AMD-070;

(9) the entry inhibitor SP01A;

(10) the gp120 inhibitor BMS-488043;

(11) the G6PD and NADH-oxidase inhibitor immunitin;

(12) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

(13) CD4 attachment inhibitors selected from the group consisting of ibalizumab (TMB-355) and BMS-068 (BMS-663068);

(14) pharmacokinetic enhancers selected from the group consisting of cobicistat and SPI-452; and

(15) other drugs for treating HIV selected from the group consisting of BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), HRG214, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040),

and combinations thereof.

[0083] In certain embodiments, the additional therapeutic agent is selected from one or more of:

(1) Combination drugs selected from the group consisting of ATRIPLA® (efavirenz+tenofovir disoproxil fumarate +emtricitabine), COMPLERA® or EVIPLERA® (rilpivirine+tenofovir disoproxil fumarate +emtricitabine), STRIBILD® (elvitegravir+cobicistat+tenofovir disoproxil fumarate +emtricitabine), dolutegravir + abacavir sulfate +lamivudine, TRIUMEQ® (dolutegravir + abacavir + lamivudine) , lamivudine + nevirapine + zidovudine, dolutegravir+rilpivirine, dolutegravir+rilpivirine hydrochloride, atazanavir sulfate + cobicistat, atazanavir + cobicistat, darunavir + cobicistat, efavirenz + lamivudine + tenofovir disoproxil fumarate, tenofovir alafenamide hemifumarate + emtricitabine + cobicistat + elvitegravir, tenofovir alafenamide hemifumarate + emtricitabine, tenofovir alafenamide + emtricitabine, tenofovir alafenamide hemifumarate + emtricitabine + rilpivirine, tenofovir alafenamide + emtricitabine + rilpivirine , Vacc-4x + romidepsin, darunavir + tenofovir alafenamide hemifumarate+ emtricitabine + cobicistat, APH-0812, raltegravir + lamivudine, KALETRA® (ALUVIA®, lopinavir+ritonavir), atazanavir sulfate + ritonavir, COMBIVIR® (zidovudine+lamivudine, AZT+3TC), EPZICOM® (Kivexa®, abacavir sulfate +lamivudine, ABC+3TC), TRIZIVIR® (abacavir sulfate+zidovudine+lamivudine, ABC+AZT+3TC), TRUVADA® (tenofovir disoproxil fumarate +emtricitabine, TDF+FTC), doravirine + lamivudine + tenofovir disoproxil fumarate, doravirine + lamivudine + tenofovir disoproxil, tenofovir + lamivudine and lamivudine + tenofovir disoproxil fumarate;

(2) HIV protease inhibitors selected from the group consisting of amprenavir, atazanavir, fosamprenavir, fosamprenavir calcium, indinavir, indinavir sulfate, lopinavir, ritonavir, nelfinavir, nelfinavir mesylate, saquinavir, saquinavir mesylate, tipranavir, brecanavir, darunavir, DG-17, TMB-657 (PPL-100) and TMC-310911;

(3) HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase selected from the group consisting of delavirdine, delavirdine mesylate, nevirapine, etravirine, dapivirine, doravirine, rilpivirine, efavirenz, KM-023, VM-1500, lentinan and AIC-

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(4) HIV nucleoside or nucleotide inhibitors of reverse transcriptase selected from the group consisting of VIDEX® and VIDEX® EC (didanosine, ddI), zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, censavudine, abacavir, abacavir sulfate, amdoxovir, elvucitabine, alovudine, phosphazid, fozivudine tidoxil, apricitabine, amdoxovir , KP-1461, fosalvudine tidoxil, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, tenofovir alafenamide hemifumarate, tenofovir alafenamide fumarate, adefovir, adefovir dipivoxil, and festinavir;

(5) HIV integrase inhibitors selected from the group consisting of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, raltegravir, elvitegravir, dolutegravir and cabotegravir;

(6) HIV non-catalytic site, or allosteric, integrase inhibitors (NCINI) selected from the group consisting of CX-05168, CX-05045 and CX-14442;

(7) HIV gp41 inhibitors selected from the group consisting of enfuvirtide, sifuvirtide and albuvirtide;

(8) HIV entry inhibitors selected from the group consisting of cenicriviroc;

(9) HIV gp120 inhibitors selected from the group consisting of Radha-108 (Receptol) and BMS-663068;

(10) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, Adaptavir (RAP-101), nifeviroc (TD-0232), TD-0680, and vMIP (Haimipu);

(11) CD4 attachment inhibitors selected from the group consisting of ibalizumab;

(12) CXCR4 inhibitors selected from the group consisting of plerixafor, ALT-1188, vMIP and Haimipu;

(13) Pharmacokinetic enhancers selected from the group consisting of cobicistat and ritonavir;

(14) Immune-based therapies selected from the group consisting of dermaVir, interleukin-7, plaquenil (hydroxychloroquine), proleukin (aldesleukin, IL-2), interferon alfa, interferon alfa-2b, interferon alfa-n3, pegylated interferon alfa, interferon gamma, hydroxyurea, mycophenolate mofetil (MPA) and its ester derivative mycophenolate mofetil (MMF), WF-10, ribavirin, IL-2, IL-12, polymer polyethyleneimine (PEI), Gepon, VGV-1, MOR-22, BMS-936559, toll-like receptors modulators (tlr1, tlr2, tlr3, tlr4, tlr5, tlr6, tlr7, tlr8, tlr9, tlr10, tlr11, tlr12 and tlr13), rintatolimod and IR-103;

(15) HIV vaccines selected from the group consisting of peptide vaccines, recombinant subunit protein vaccines, live vector vaccines, DNA vaccines, virus-like particle vaccines (pseudovirion vaccine), CD4-derived peptide vaccines, vaccine combinations, rgp120 (AIDSVAX), ALVAC HIV (vCP1521)/AIDSVAX B/E (gp120) (RV144), monomeric gp120 HIV-1 subtype C vaccine (Novartis), Remune, ITV-1, Contre Vir, Ad5-ENVA-48, DCVax-001 (CDX-2401), PEP-6409,Vacc-4x, Vacc-C5, VAC-3S, multiclade DNA recombinant adenovirus-5 (rAd5), Pennvax-G, VRC-HIV MAB060-00-AB, AVX-101, Tat Oyi vaccine, AVX-201, HIV-LAMP-vax, Ad35, Ad35-GRIN, NAcGM3/VSSP ISA-51, poly-ICLC adjuvanted vaccines, TatImmune, GTU-multiHIV (FIT-06), AGS-004, gp140[delta]V2.TV1+ MF-59, rVSVIN HIV-1 gag vaccine, SeV-Gag vaccine, AT-20, DNK-4, Ad35-GRIN/ENV, TBC-M4, HIVAX , HIVAX-2, NYVAC-HIV-PT1, NYVAC-HIV-PT4, DNA-HIV-PT123, rAAV1-PG9DP, GOVX-B11, GOVX-B21, ThV-01, TUTI-16, VGX-3300, TVI-HIV-1, Ad-4 (Ad4-env Clade C + Ad4-mGag), EN41-UGR7C, EN41-FPA2, ProVaxTat, TL-01, SAV-001, AE-H, MYM-V101, CombiHIVvac, ADVAX, MYM-V201, MVA-CMDR, ETV-01, CDX-1401, rcAd26.MOS1.HIV-Env and DNA-Ad5 gag/pol/nef/nev (HVTN505);

(16) HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins (such as DARTs®, Duobodies®, Bites®, XmAbs®, TandAbs ®, Fab derivatives) including BMS-936559, TMB-360 and those targeting HIV gp120 or gp41 selected from the group consisting of bavituximab, UB-421, C2F5, C2G12, C4E10, C2F5+C2G12+C4E10, 3-BNC-117 , PGT145, PGT121, MDX010 (ipilimumab),

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VRC01, A32, 7B2, 10E8, VRC-07-523 and VRC07;

(17) latency reversing agents selected from the group consisting of Histone deacetylase inhibitors such as Romidepsin, vorinostat, panobinostat; Proteasome inhibitors such as Velcade; protein kinase C (PKC) activators such as Indolactam, Prostratin, Ingenol B and DAG-lactones, Ionomycin, GSK-343, PMA, SAHA, BRD4 inhibitors, IL-15, JQ1, disulfram, and amphotericin B;

(18) HIV nucleocapsid p7 (NCp7) inhibitors selected from the group consisting of azodicarbonamide;

(19) HIV maturation inhibitors selected from the group consisting of BMS-955176 and GSK-2838232;

(20) PI3K inhibitors selected from the group consisting of idelalisib, AZD-8186, buparlisib, CLR-457, pictilisib, neratinib, rigosertib, rigosertib sodium, BN-3342, TGR-1202, alpelisib, duvelisib, UCB-5857, taselisib, XL-765, gedatolisib, VS-5584, copanlisib, CAI orotate, perifosine, RG-7666, GSK-2636771, DS-7423, panulisib, GSK-2269557, GSK-2126458, CUDC-907, PQR-309, INCB-040093, pilaralisib, BAY-1082439, puquitinib mesylate, SAR-245409, AMG-319, RP-6530, ZSTK-474, MLN-1117, SF-1126, RV-1729, sonolisib, LY-3023414, SAR-260301 and CLR-1401;

(21) the compounds disclosed in WO 2004/096286 (Gilead Sciences), WO 2006/110157 (Gilead Sciences), WO 2006/015261 (Gilead Sciences), WO 2013/006738 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), US20140221380 (Japan Tobacco), US20140221378 (Japan Tobacco), WO 2013/006792 (Pharma Resources), WO 2009/062285 (Boehringer Ingelheim), WO 2010/130034 (Boehringer Ingelheim), WO 2013/091096A1 (Boehringer Ingelheim), WO 2013/159064 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO2012/003497 (Gilead Sciences), WO2014/100323 (Gilead Sciences), WO2012/145728 (Gilead Sciences), WO2013/159064 (Gilead Sciences) and WO 2012/003498 (Gilead Sciences); and

(22) other drugs for treating HIV selected from the group consisting of BanLec, MK-8507, AG-1105, TR-452, MK-8591, REP 9, CYT-107, alisporivir, NOV-205, IND-

02, metenkefalin, PGN-007, Acemannan, Gamimune, Proiastin, 1,5-dicaffeoylquinic acid, BIT-225, RPI-MN, VSSP, Hiviral, IMO-3100, SB-728-T, RPI-MN, VIR-576, HGTV-43, MK-1376, rHIV7-shl-TAR-CCR5RZ, MazF gene therapy, BlockAide, ABX-464, SCY-635, naltrexone, AAV-eCD4-Ig gene therapy and PA-1050040 (PA-040);

and combinations thereof.

[0084] In certain embodiments, a compound disclosed herein is combined with two, three, four or more additional therapeutic agents. In certain embodiments, a compound disclosed herein is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein is combined with four additional therapeutic agents. The two, three four or more additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, or they can be selected from different classes of therapeutic agents. In a specific embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In a further embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer. In another embodiment, a compound disclosed herein is combined with two HIV nucleoside or nucleotide inhibitors of reverse transcriptase.

[0085] In certain embodiments, a compound disclosed herein, is combined with one, two, three, four or more additional therapeutic agents. In certain embodiments, a compound disclosed herein is combined with one additional therapeutic agent. In certain embodiments, a compound disclosed herein is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein is combined with four additional therapeutic agents. The one, two, three, four or more additional therapeutic agents

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can be different therapeutic agents selected from the same class of therapeutic agents, and/or they can be selected from different classes of therapeutic agents. In a specific embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In a further embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer. In certain embodiments, a compound disclosed herein is combined with at least one HIV nucleoside inhibitor of reverse transcriptase, an integrase inhibitor, and a pharmacokinetic enhancer. In another embodiment, a compound disclosed herein is combined with two HIV nucleoside or nucleotide inhibitors of reverse transcriptase.

[0086] In certain embodiments, a compound disclosed herein is combined with at least one HIV nucleoside inhibitor of reverse transcriptase, an integrase inhibitor, and a pharmacokinetic enhancer.

[0087] In a particular embodiment, a compound disclosed herein is combined with abacavir, abacavir sulfate, tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

[0088] In a particular embodiment, a compound disclosed herein is combined with tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

[0089] In a particular embodiment, a compound disclosed herein is combined with a first additional therapeutic agent selected from the group consisting of: abacavir, abacavir sulfate, tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate and a second additional therapeutic agent selected from the group consisting of emtricitibine and lamivudine.

[0090] In a particular embodiment, a compound disclosed herein is combined with a first additional therapeutic agent selected from the group consisting of: tenofovir, tenofovir

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disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitibine.

[0091] In a particular embodiment, a compound disclosed herein is combined with one, two, three, four or more additional therapeutic agents selected from Triumeq® (dolutegravir+abacavir +lamivudine), dolutegravir + abacavir sulfate + lamivudine, raltegravir, raltegravir + lamivudine, Truvada® (tenofovir disoproxil fumarate +emtricitabine, TDF+FTC), maraviroc, enfuvirtide , Epzicom® (Livexa®, abacavir sulfate +lamivudine, ABC+3TC), Trizivir® (abacavir sulfate+zidovudine+lamivudine, ABC+AZT+3TC), adefovir, adefovir dipivoxil, Stribild ® (elvitegravir+cobicistat+tenofovir disoproxil fumarate +emtricitabine), rilpivirine, rilpivirine hydrochloride, Complera® (Eviplera®, rilpivirine+tenofovir disoproxil fumarate +emtricitabine), Cobicistat, atazanavir sulfate + cobicistat, atazanavir + cobicistat, darunavir + cobicistat, Atripla® (efavirenz+tenofovir disoproxil fumarate +emtricitabine), atazanavir, atazanavir sulfate, dolutegravir, elvitegravir, Aluvia® (Kaletra®, lopinavir+ritonavir), ritonavir , emtricitabine , atazanavir sulfate + ritonavir, darunavir, lamivudine, Prolastin, fosamprenavir, fosamprenavir calcium, efavirenz, Combivir® (zidovudine+lamivudine, AZT+3TC), etravirine, nelfinavir, nelfinavir mesylate, interferon, didanosine, stavudine, indinavir, indinavir sulfate, tenofovir + lamivudine, zidovudine, nevirapine, saquinavir, saquinavir mesylate, aldesleukin, zalcitabine, tipranavir, amprenavir, delavirdine, delavirdine mesylate, Radha-108 (Receptol), Hiviral, lamivudine + tenofovir disoproxil fumarate, efavirenz + lamivudine + tenofovir disoproxil fumarate , phosphazid, lamivudine + nevirapine + zidovudine, abacavir, abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, darunavir + cobicistat, atazanavir sulfate + cobicistat, atazanavir + cobicistat, tenofovir alafenamide and tenofovir alafenamide hemifumarate.

[0092] In a particular embodiment, a compound disclosed herein is combined with abacavir, abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide or tenofovir alafenamide hemifumarate.

[0093] In a particular embodiment, a compound disclosed herein is combined with tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

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[0094] In a particular embodiment, a compound disclosed herein is combined with a first additional therapeutic agent selected from the group consisting of: abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate and a second additional therapeutic agent selected from the group consisting of emtricitabine and lamivudine.

[0095] In a particular embodiment, a compound disclosed herein is combined with a first additional therapeutic agent selected from the group consisting of: tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine.

[0096] In certain embodiments, a compound disclosed herein is combined with 5-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 5-10; 5-15; 5-20; 5-25; 25-30; 20-30; 15-30; or 10-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 10 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of formula (II)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 50 mg to 500 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[0097] In certain embodiments, a compound disclosed herein is combined with 200-400 mg tenofovir disproxil, tenofovir disoproxil fumarate, or tenofovir disoproxil hemifumarate and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 200-250; 200-300; 200-350; 250-350; 250-400; 350-400; 300-400; or 250-400 mg tenofovir disoproxil, tenofovir disoproxil fumarate, or tenofovir disoproxil hemifumarate and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 300 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil and 200 mg emtricitabine. A compound as disclosed

herein (e.g., a compound of formula (II)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 50 mg to 500 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[0098] In certain embodiments, when a compound disclosed herein is combined with one or more additional therapeutic agents as described above, the components of the composition are administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

[0099] In certain embodiments, a compound disclosed herein is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a patient, for example as a solid dosage form for oral administration.

[0100] In certain embodiments, a compound disclosed herein is administered with one or more additional therapeutic agents. Co-administration of a compound disclosed herein with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein and one or more additional therapeutic agents, such that therapeutically effective amounts of the compound disclosed herein and one or more additional therapeutic agents are both present in the body of the patient.

[0101] Co-administration includes administration of unit dosages of the compounds disclosed herein before or after administration of unit dosages of one or more additional therapeutic agents, for example, administration of the compound disclosed herein within seconds, minutes, or hours of the administration of one or more additional therapeutic agents. For example, in some embodiments, a unit dose of a compound disclosed herein is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, in other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound disclosed herein within seconds or minutes. In some embodiments, a unit dose of a compound disclosed herein is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound disclosed herein.

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XRPD Data

[0102] In certain embodiments, the crystalline forms are characterized by the interlattice plane intervals determined by an X-ray powder diffraction pattern (XRPD). The diffractogram of XRPD is typically represented by a diagram plotting the intensity of the peaks versus the location of the peaks, i.e., diffraction angle 2θ (two-theta) in degrees. The intensities are often given in parenthesis with the following abbreviations: very strong = vst; strong = st; medium = m; weak = w; and very weak = vw. The characteristic peaks of a given XRPD can be selected according to the peak locations and their relative intensity to conveniently distinguish this crystalline structure from others.

[0103] Those skilled in the art recognize that the measurements of the XRPD peak locations and/or intensity for a given crystalline form of the same compound will vary within a margin of error. The values of degree 2θ allow appropriate error margins. Typically, the error margins are represented by "±". For example, the degree 2θ of about "8.7±0.3" denotes a range from about 8.7+0.3, i.e., about 9.0, to about 8.7-0.3, i.e., about 8.4. Depending on the sample preparation techniques, the calibration techniques applied to the instruments, human operational variation, and etc, those skilled in the art recognize that the appropriate error of margins for a XRPD can be ±0.5; ±0.4; ±0.3; ±0.2; ±0.1; ±0.05; or less. In certain embodiments of the invention, the XRPD margin of error is ±0.2.

[0104] Additional details of the methods and equipment used for the XRPD analysis are described in the Examples section.

[0105] The XRPD peaks for the crystalline forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate (Formula II) of the present invention can be found below in Table 1

[0106] Table 1: XRPD peaks for crystalline forms of Formula II Form I

Formula II Form I	
Peak Position [°2θ]	Relative Intensity [%]
5.5	100.0
16.1	87.3
17.9	22.4
19.5	38.0
22.1	61.8
22.5	42.2
23.3	60.4
26.6	27.3
28.5	42.9

Preparation of the Polymorphs

[0107] One method of synthesizing (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (*e.g.* a compound of Formula (I)) has been previously described in PCT Publication No. WO2014/100323. This reference is hereby incorporated herein by reference in its entirety, and specifically with respect to the synthesis of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide. One method of synthesizing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate (*e.g.* a compound of Formula (II)) is described herein.

[0108] For example, in one aspect, provided is a method of producing a composition comprising one or more polymorphs of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the method comprises combining a compound of Formula (I) with a suitable solvent or a mixture of suitable solvents to produce a composition comprising one or more polymorphs of the compound of Formula (II). In another aspect, provided is another method of producing a composition comprising one or more polymorphs of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-

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trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the method comprises combining sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate with a suitable solvent or a mixture of suitable solvents.

[0109] The choice of a particular solvent or combination of solvents affects the formation favoring one polymorphic form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate over another. Solvents suitable for polymorph formation may include, for example, methanol, ethanol, water, isopropyl acetate, acetonitrile, tetrahydrofuran, methyl isobutyl ketone, and any mixtures thereof.

[0110] In another aspect, provided is also one or more polymorphs of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate produced according to any of the methods described herein.

[0111] It should be understood that the methods for preparing the polymorphs described herein (including any polymorphic Form I) may yield quantity and quality differences compared to the methods for preparing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate produced on laboratory scale.

Formula II, Form I

[0112] In one embodiment, provided is a method of producing a composition comprising polymorphic Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the method comprises combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a sodium base (e.g. sodium hydroxide) in a solvent to produce a composition comprising polymorphic Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the solvent is selected

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from the group consisting of ethanol, dimethylformamide, and any mixture thereof. In an embodiment, the solvent is a mixture of ethanol and dimethylformamide.

[0113] Provided is also polymorphic Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate prepared by combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a sodium base (*e.g.* sodium hydroxide) in a solvent, wherein the solvent is selected from the group consisting of ethanol, dimethylformamide, and any mixture thereof. In an embodiment, the solvent is a mixture of ethanol and dimethylformamide.

Uses in Manufacturing of Drug Product

Formula II

[0114] Provided are also a use of the polymorphs described herein in the manufacture of a drug product. The one or more of the polymorphic forms described herein (*e.g.*, polymorphic Form I) may be used as an intermediate in the manufacturing process to produce the drug product.

[0115] In certain embodiments, Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate are used in the manufacture of an active pharmaceutical ingredient.

Articles of Manufacture and Kits

[0116] Compositions comprising one or more of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate and formulated in one or more pharmaceutically acceptable carriers, excipients or other ingredients can be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition. Accordingly, there also is contemplated an article of manufacture, such as a container comprising a dosage form of one or more of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-

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methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, and a label containing instructions for use of the compound(s).

[0117] In some embodiments, the article of manufacture is a container comprising a dosage form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, and one or more pharmaceutically acceptable carriers, excipients or other ingredients. In one embodiment of the articles of manufacture described herein, the dosage form is a tablet.

[0118] Kits also are contemplated. For example, a kit can comprise a dosage form of a pharmaceutical composition and a package insert containing instructions for use of the composition in treatment of a medical condition. The instructions for use in the kit may be for treating HIV. In certain embodiments, the instructions for use in the kit may be for treating HIV.

[0119] In certain embodiments, the polymorphic and solvate forms described herein may potentially exhibit improved properties. For example, in certain embodiments, the polymorphic and solvate forms described herein may potentially exhibit improved stability. Such improved stability could have a potentially beneficial impact on the manufacture of the Compound of Formula I, such as for example offering the ability to store process intermediate for extended periods of time. Improved stability could also potentially benefit a composition or pharmaceutical composition of the Compound of Formula II. In certain embodiments, the polymorphic and solvate forms described herein may also potentially result in improved yield of the Compound of Formula II, or potentially result in an improvement of the quality of the Compound of Formula II. In certain embodiments, the polymorphic and solvate forms described herein may also exhibit improved pharmacokinetic properties and/or potentially improved bioavailability.

Methods

Synthesis

Sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate (Formula II)

[0120] (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (20 g) and ethanol (80 mL) were added to a reaction vessel and warmed to about 75 °C. Aqueous sodium hydroxide (22 mL 2 M solution) was added over approximately 30 minutes, after which the slurry was cooled to approximately 20 °C over approximately one hour. Sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was collected by filtration, washed with EtOH (50 mL) and dried under vacuum.

[0121] ^{1}H NMR (400 MHz, DMSO-d6) δ 10.63 (t, J = 5.8 Hz, 1H), 7.88 (s, 1H), 7.29 – 7.07 (m, 2H), 5.20 (dd, J = 8.6, 3.6 Hz, 1H), 5.09 (t, J = 4.1 Hz, 1H), 4.52 (m, 3H), 4.35 (dd, J = 12.8, 3.6 Hz, 1H), 3.87 (dd, J = 12.7, 8.7 Hz, 1H), 2.03 – 1.80 (m, 3H), 1.76-1.64 (m, 2H), 1.50 – 1.40 (m, 1H).

Characterization

[0122] Sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was characterized by various analytical techniques, including X-ray powder diffraction pattern (XPPD), differential scanning calorimetry (DSC), thermographic analysis (TGA), and dynamic vapor sorption (DVS) using the procedures described below.

[0123] *X-Ray Powder Diffraction:* XRPD analysis was conducted on a diffractometer (PANanalytical XPERT-PRO, PANanalytical B.V., Almelo, Netherlands) using copper radiation (Cu Kα, λ = 1.5418 Å). Samples were prepared for analysis by depositing the powdered sample in the center of an aluminum holder equipped with a zero background plate. The generator was operated at a voltage of 45 kV and amperage of 40 mA. Slits used were Soller 0.02 rad., antiscatter 1.0°, and divergence. The sample rotation speed was 2 sec. Scans were performed from 2 to 40° 2θ during 5-15 min with a step size of 0.0167° 2θ. Data analysis was performed by X'Pert Highscore version 2.2c (PANalytical B.V., Almelo, Netherlands) and X'Pert data viewer version 1.2d (PANalytical B.V., Almelo, Netherlands).

[0124] The XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is represented in Figure

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1. The calculated XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I represented in Figure 1 was calculated by using Mercury 3.1 Development (Build RC5). Single crystal data for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was input into Mercury 3.1 Development (Build RC5) to calculate the XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I. Bulk material, such as stoichiometry arity between the temperature was obtained on a Rigaku Miniflex II XRD using power settings of 40kV, 15mA, scan speed of 2.0000 degrees per minute, a Miniflex 300/600 goniometer and an ASC-6 attachment, a scan range of 3.000 to 40.000 degrees, an incident slit of 1.250 degress, a length limiting slit of 10.0 mm, and SC-70 detector, a receiving slit #1 of 1.250 degrees, continuous scan mode, and a receiving slit #2 of 0.3mm. The sample was prepared by smoothing about 20 mg of solids on a silicon disk mounted in a metal holder. Acquisition temperature was ~21 °C.

[0125] The XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is further represented in Figure 8. The calculated XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I represented in Figure 8 was calculated by using Mercury 3.1 Development (Build RC5). Single crystal data for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was input into Mercury 3.1 Development (Build RC5) to calculate the XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I. Bulk material, such as stoichiometry arity between the temperature was obtained on a Rigaku Miniflex II XRD using power settings of 40kV, 15mA, scan speed of 2.0000 degrees per minute, a Miniflex 300/600 goniometer and an ASC-6 attachment, a scan range of 3.000 to 40.000 degrees, an incident slit of 1.250 degress, a length limiting slit of 10.0 mm, and SC-70 detector, a receiving slit #1 of 1.250 degrees, continuous scan mode, and a receiving slit #2 of

0.3mm. The sample was prepared by smoothing about 20 mg of solids on a silicon disk mounted in a metal holder. Acquisition temperature was ~21 °C.

[0126] Figure 8 compares the calculated XRPD pattern of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I to the experimental XRPD pattern of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I. The comparison shows the degree to which the calculated XRPD and experimental XRPD agree. Strong agreement indicates the solved crystal structure is also the crystal structure of the material analyzed directly by XRPD. This determination can support orthogonal data about the composition of the bulk material, such as stoichiometry.

[0127] XRPD peaks are found in Table 1 above.

[0128] *Differential scanning calorimetry:* Thermal properties of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I were evaluated using a Differential Scanning Calorimetry (DSC) instrument (TA Q1000, TA Instruments, New Castle, DE, USA). Approximately 1 to 10 mg of solid sample was placed in a standard aluminum pan vented with a pinhole for each experiment and heated at a rate of 10 °C/min under a 50 mL/min nitrogen purge. Data analysis was conducted using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE, USA). Heat of fusion analysis was conducted by sigmoidal integration of the endothermic melting peak.

[0129] The DSC for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is represented in Figure 2.

[0130] *Thermogravimetric analysis:* Thermogravimetric analysis (TGA) of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was performed on a TGA instrument (TA Q500, TA Instruments, New Castle, DE, USA). Approximately 1 to 10 mg of solid sample was placed in an open aluminum pan for each experiment and heated at a rate of 10 °C/min under a 60 mL/min nitrogen purge using. Data analysis was conducted

using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE, USA).

[0131] The TGA for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is represented in Figure 3.

[0132] *Dynamic vapor sorption:* The hygroscopicity of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was evaluated at about 25 °C using a dynamic vapor sorption (DVS) instrument (TGA Q5000 TA Instruments, New Castle, DE). Water adsorption and desorption were studied as a function of relative humidity (RH) over the range of 0 to 90% at room temperature. The humidity in the chamber was increased from the initial level 50% RH to 60% RH and held until the solid and atmosphere reached equilibration. The equilibrium test was continued until passed or expired after 10 hours. At this point, RH was raised 10% higher and the process was repeated until 90% RH was reached and equilibrated. During this period, the water sorption was monitored. For desorption, the relative humidity was decreased in a similar manner to measure a full sorption/desorption cycle. The cycle was optionally repeated. All experiments were operated in dm/dt mode (mass variation over time) to determine the equilibration endpoint. Approximately 3 mg of solid sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate was used. Data analysis was conducted using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE, USA).

[0133] The DVS for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is represented in Figure 4.

[0134] The indexing data for Formula II Form I is summarized in Table 2 below.

Table 2: Indexing Data for Formula II Form I

Form and Identification	Solvent	Unit Cell Dimensions					
		Distance (Å)			Angle (°)		
		a	b	c	α	β	γ
Formula II Form I	methanol	9.105	13.986	31.384	90	90	90

[0135] The single crystal X-ray diffraction studies were carried out on a Bruker APEX II Ultra diffractometer equipped with Mo K_α radiation ($\lambda = 0.71073$ Å). Crystals of the subject compound were cut into a 0.22 x 0.18 x 0.04 mm section and mounted on a Cryoloop with Paratone-N oil. Data were collected in a nitrogen gas stream at 100 (2) K. A total of 15725 reflections were collected covering the indices, $-9 \leq h \leq 10$, $-13 \leq k \leq 16$, $-37 \leq l \leq 36$. 7163 reflections were found to be symmetry independent, with a R_{int} of 0.0682. Indexing and unit-cell refinement indicated an orthorhombic lattice. The space group, which was uniquely defined by the systematic absences in the data, was found to be $P2_12_12_1$. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model compatible with the proposed structure.

[0136] All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 2A. The absolute stereochemistry was set to conform to previously studied samples of the same compound.

[0137] The single crystal X-ray crystallography data for Formula II Form I is summarized in Table 2A below.

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Table 2A: Single Crystal Data for Formula II, Form I

C42 H34 F6 N6 Na2 O10	Acquisition Temp.	Space Group	Z	Unit Cell Dimensions					
	100(2) K	P212121	4	Distance (Å)			Angle (°)		
Form and Identification	Solvent	Solvent in lattice	Density (Mg/m^3)	a	b	c	α	β	γ
Formula II Form I	Ethanol/DMF	none	1.614	8.9561 (10)	13.9202 (14)	31.115 (3)	90	90	90

Dissolution Profile

[0138] The intrinsic dissolution profile of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate (Formula II) Form I of the present invention and the intrinsic dissolution profiles of Form I and Form III of Formula I, the free acid, (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (disclosed in the co-pending United States Provisional Application 62/015,238 filed on June 20, 2014 titled CRYSTALLINE FORMS OF (2R,5S,13AR)-8-HYDROXY-7,9-DIOXO-N-(2,4,6-TRIFLUOROBENZYL)-2,3,4,5,7,9,13,13A-OCTAHYDRO-2,5-METHANOPYRIDO[1',2':4,5]PYRAZINO[2,1-B][1,3]OXAZEPINE-10-CARBOXAMIDE), were measured by characterizing API dissolution from a constant surface area. Approximately 150 mg of the drug substance was compressed at 1500 psi for approximately 3 seconds using a hydraulic press (Carver Press, Fred Carver, NJ, USA). The compressed drug substance formed a flat disk (surface area ~0.49 cm^2), which was mounted onto a dissolution apparatus (VanKel Industries Inc., Edison, NJ, VK7000, W1120A-0288). The rotating disk (100 rpm) was then lowered into the dissolution medium (500 mL of 0.01N HCl) which was equilibrated to 37±1°C. Samples were pulled at pre-determined time points and drug concentrations were measured using an appropriate UPLC-UV method. The intrinsic dissolution rate constant (K) was calculated using the following equation:

$$C = \frac{KA}{V}t$$

[0139] Where C is the concentration of the active at time t, A is the surface area of the

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tablet (~0.49 cm^2) and V is the volume of the media (500 mL). Note that the term active as used herein refers to the parent molecule, whose structure is shared by both Formula I and Formula II.

[0140] The dissolution profiles can be found in Figure 5.

Solubility

[0141] The solubility of the sodium form of the present invention and the free acid, (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form III in biorelevant media was determined at room temperature as a function of time. Solubility was determined in the following biorelevant media: 0.1 mM Fasted-State Simulated Gastric Fluid (FaSSGF) pH 1.6 (0.08 mM taurocholate, 0.02 mM lecithin, 34.2 mM NaCl); 18.75 mM Fed-State Simulated Intestinal Fluid (FeSSIF) pH 5 (15 mM taurocholate, 3.75 mM lecithin, 0.12 M NaCl); and 3.75mM Fasted-State Simulated Intestinal Fluid (FaSSIF) pH 5 (3 mM taurocholate, 0.75 mM lecithin, 0.10 M NaCl). Approximately 20 mg of the drug substance was mixed on a magnetic stir-plate in 50 mL of biorelevant media. Samples (~1 mL) were pulled every 5-10 min for 2 hours. The samples were immediately filtered/centrifuged for 10 min in a Spin-X tube equipped with a 0.45 µm nylon filter. The resulting filtrate was analyzed using an appropriate UPLC-UV method.

[0142] The solubility profiles in FaSSGF can be found in Figure 6. The solubility profiles in FeSSIF and FaSSIF can be found in Figure 7.

Bioavailability

[0143] The bioavailability of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate (Formula II) Form I was compared to the bioavailability of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (Formula I) Form III.

[0144] Each dosing group consisted of 6 male, non-naïve purebred beagle dogs. At dosing, the animals weighed between 10 to 13 kg. The animals were fasted overnight prior to

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dose administration and up to 4 hr after dosing. Each subject was pre-treated with pentagastrin (6 µg/kg) and dosed 30 minutes later with a single 25 mg strength tablet of Formula II Form I or Formula I Form III. Each subject was given 10 mL of water to aid in swallowing.

[0145] Serial venous blood samples (approximately 1 mL each) were taken from each animal at 0, 0.250, 0.483, 0.583, 0.750, 1.00, 1.50, 2.00, 4.00, 8.00, 12.0, and 24.0 hours after dosing. The blood samples were collected into Vacutainer™ tubes containing EDTA-K2 as the anti-coagulant and were immediately placed on wet ice pending centrifugation for plasma. An LC/MS/MS method was used to measure the concentration of the test compound in plasma. An aliquot of 100 µL of each plasma sample was added to a clean 96 well plate, and 400 µL of cold acetonitrile/internal standard solution (ACN)/(ISTD) was added. After protein precipitation, an aliquot of 110 µL of the supernatant was transferred to a clean 96-well plate and diluted with 300 µL of water. An aliquot of 25 µL of the above solution was injected into a TSQ Quantum Ultra LC/MS/MS system utilizing a Hypersil Gold C_{18} HPLC column (50 X 3.0 mm, 5 µm; Thermo-Hypersil Part # 25105-053030). An Agilent 1200 series binary pump (P/N G1312A Bin Pump) was used for elution and separation, and an HTS Pal autosampler (LEAP Technologies, Carrboro, NC) was used for sample injection. A TSQ Quantum Ultra triple quadrupole mass spectrometer was utilized in selective reaction monitoring mode (Thermo Finnigan, San Jose, CA). Liquid chromatography was performed using two mobile phases: mobile phase A contained 1% acetonitrile in 2.5 mM ammonium formate aqueous solution with pH of 3.0, and mobile phase B contained 90% acetonitrile in 10 mM ammonium formate with pH of 4.6. Non-compartmental pharmacokinetic analysis was performed on the plasma concentration-time data. The resulting data are shown in Table 3: F (%) refers to oral bioavailability; AUC refers to area under the curve and is a measure of total plasma exposure of the indicated compound; C_{max} refers to the peak plasma concentration of the compound after administration.

Table 3: Bioavailability of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I and (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form III.

Form	Formulation	%F	AUC_{inf} (uM x hr)	C_{max} (uM)
Formula I Form III	Dry Granulation[1]	10 ± 6	27 ± 13	6 ± 2
Formula II Form I	Dry Granulation[2]	28 ± 7	71 ± 16	13 ± 1

[1] *Tablet*: 30% active, 56% microcrystalline cellulose, 13% croscarmellose sodium, 1% magnesium stearate
[2] *Tablet*: 30% active, 56% microcrystalline cellulose, 13% croscarmellose sodium, 1% magnesium stearate

Stability

[0146] The stability of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was tested. As seen in Table 4, below, the compound is stable after four weeks of storage under accelerated conditions. In Table 5, AN refers to area normalization and is the relative peak area of the active with respect to other impurities and components contained in the sample. LS refers to labile strength and is the amount of active present relative to the theoretical amount.

Table 4: Stability of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I

Storage Conditions	Storage Time (weeks)	%AN	%LS
Starting material	0	94.4 ± 0.1	99.8 ± 0.1
40°C (closed)	1	95.2 ± 0.3	108.0 ± 0.2
	2	94.4 ± 0.1	102.4 ± 0.1
	4	94.4 ± 0.0	97.0 ± 0.0
40°C/75% RH (open)	1	94.9 ± 0.1	103.3 ± 6.9
	2	94.4 ± 0.0	108.5 ± 0.4
	4	94.4 ± 0.0	102.9 ± 0.1
25°C/60% RH (open)	1	95.0 ± 0.2	104.8 ± 0.1
	2	94.4 ± 0.1	101.6 ± 0.1
	4	94.4 ± 0.0	103.0 ± 0.8

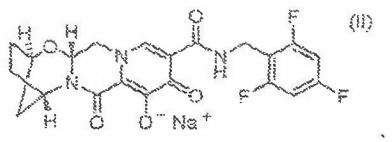
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[0147] Each of the references including all patents, patent applications and publications cited in the present application is incorporated herein by reference in its entirety, as if each of them is individually incorporated. Further, it would be appreciated that, in the above teaching of invention, the skilled in the art could make certain changes or modifications to the invention, and these equivalents would still be within the scope of the invention defined by the appended claims of the application. Each of the references including all patents, patent applications and publications cited in the present application is incorporated herein by reference in its entirety, as if each of them is individually incorporated. Further, it would be appreciated that, in the above teaching of invention, the skilled in the art could make certain changes or modifications to the invention, and these equivalents would still be within the scope of the invention defined by the appended claims of the application.

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What is Claimed:

1. A compound of Formula II:



(II)

2. The compound of claim 1, characterized by being crystalline.

3. The compound of claim 2, characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 5.5°, 16.1°, and 23.3° 2-θ ± 0.2° 2-θ.

4. The compound of claim 3, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 22.1°, and 28.5° 2-θ ± 0.2° 2-θ.

5. The compound of claim 4, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 22.5 and 19.5° 2-θ ± 0.2° 2-θ.

6. The compound of claim 5, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 26.6° and 17.9° 2-θ ± 0.2° 2-θ.

7. The compound of claim 2, characterized by an x-ray powder diffraction (XRPD) pattern substantially as set forth in Figure 1.

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8. The compound of claim 2, characterized by differential scanning calorimetry (DSC) pattern substantially as set forth in Figure 2.

9. The compound of claim 2, characterized by a dynamic vapor sorption (DVS) pattern substantially as set forth in Figure 4.

10. The compound of any one of claims 1 to 9, characterized in being partially or fully hydrated.

11. The compound of any one of claims 1 to 9, characterized in being anhydrous or essentially anhydrous.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1 to 11, and a pharmaceutically acceptable carrier or excipient.

13. The pharmaceutical composition of claim 12, further comprising one to three additional therapeutic agents.

14. The pharmaceutical composition of claim 13, wherein the additional therapeutic agents are each anti-HIV drugs.

15. The pharmaceutical composition of claim 13 or claim 14, wherein the additional therapeutic agents are each independently selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors

of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and other drugs for treating HIV.

16. The pharmaceutical composition of any one of claims 12 to 14, wherein at least two of the additional therapeutic agents are each HIV nucleoside inhibitors of reverse transcriptase.

17. The pharmaceutical composition of claim 12, further comprising tenofovir disoproxil fumarate and emtricitabine.

18. The pharmaceutical composition of claim 12, further comprising tenofovir alafenamide and emtricitabine.

19. The pharmaceutical composition of claim 12, further comprising tenofovir alafenamide hemifumarate and emtricitabine.

20. The pharmaceutical composition of any one of claims 12 to 18, wherein the pharmaceutical composition is in a unit dosage form.

21. The pharmaceutical composition of claim 20, wherein the unit dosage form is a tablet.

22 Use of a compound of any one of claims 1 to 11 for treating or prophylactically preventing an HIV infection.

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23. Use of a compound of any one of claims 1 to 11 for the manufacture of a medicament for treating or prophylactically preventing an HIV infection.

24. A compound of any one of claims 1 to 11 for use in a method for treating or prophylactically preventing an HIV infection.

25. A method for treating or prophylactically preventing an HIV infection in a human in need thereof, comprising administering to the human a therapeutically effective amount of a compound of any one of claims 1 to 11.

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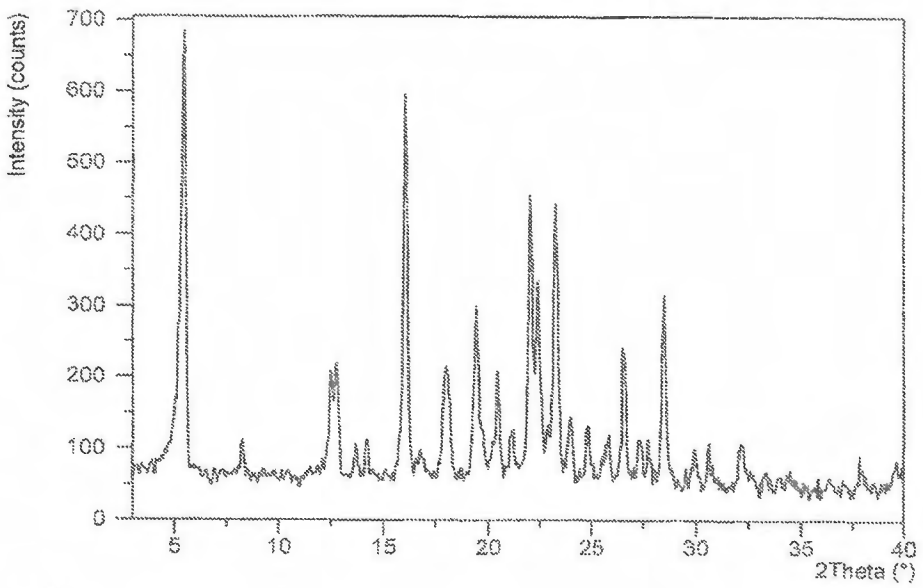

Intensity (counts)
700
600
500
400
300
200
100
0
5
10
15
20
25
30
35
40
2Theta (°)

Figure 1

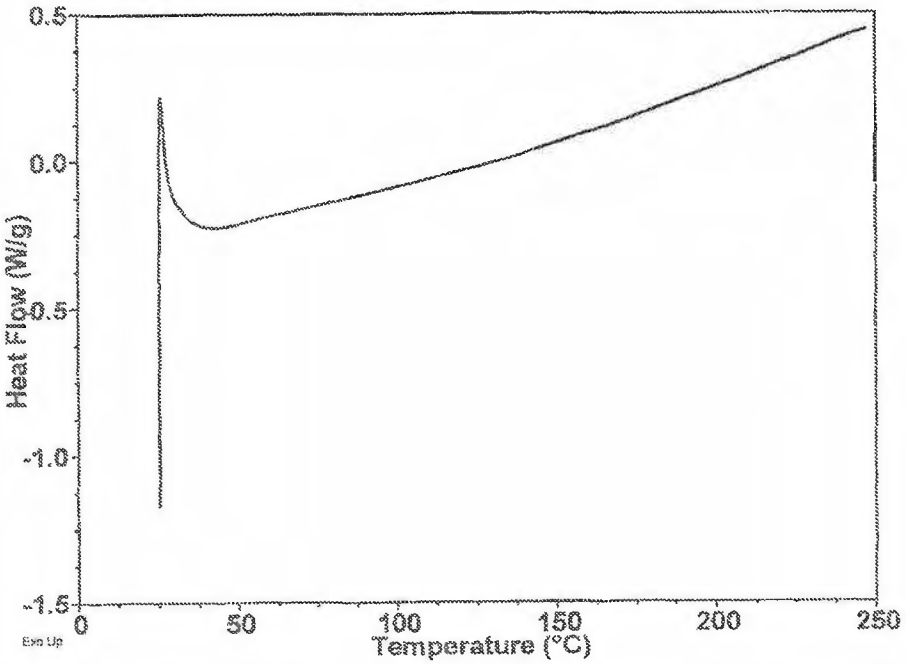

0.5
0.0
-0.5
-1.0
-1.5
Heat Flow (W/g)
Exo Up
0
50
100
150
200
250
Temperature (°C)

Figure 2

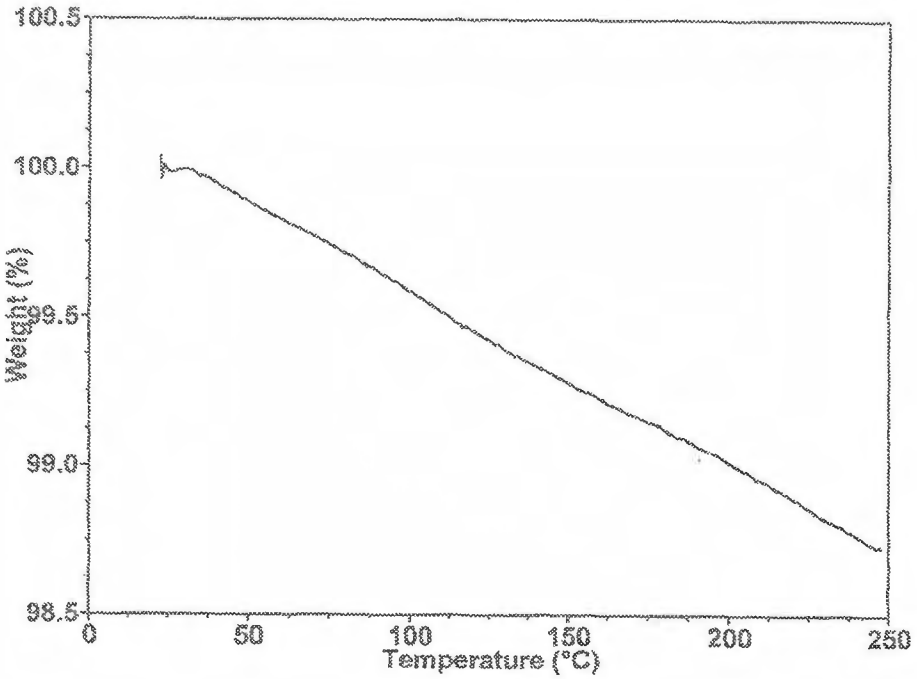

100.5
100.0
99.5
99.0
98.5
Weight (%)
0
50
100
150
200
250
Temperature (°C)

Figure 3

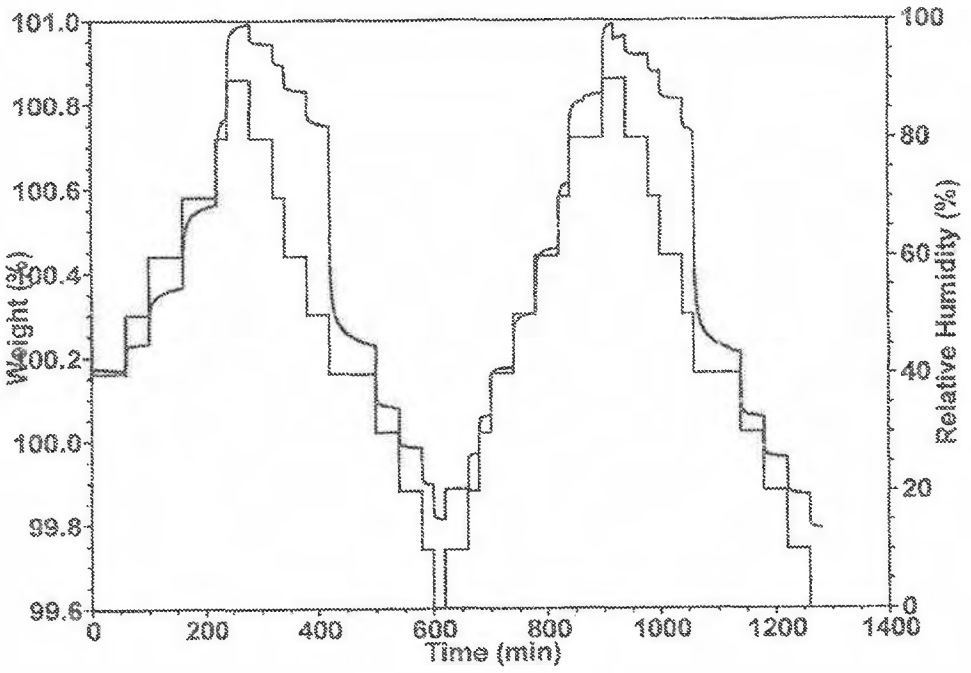

101.0
100.8
100.6
100.4
100.2
100.0
99.8
99.6
Weight (%)
0
200
400
600
800
1000
1200
1400
Time (min)
100
80
60
40
20
0
Relative Humidity (%)

Figure 4

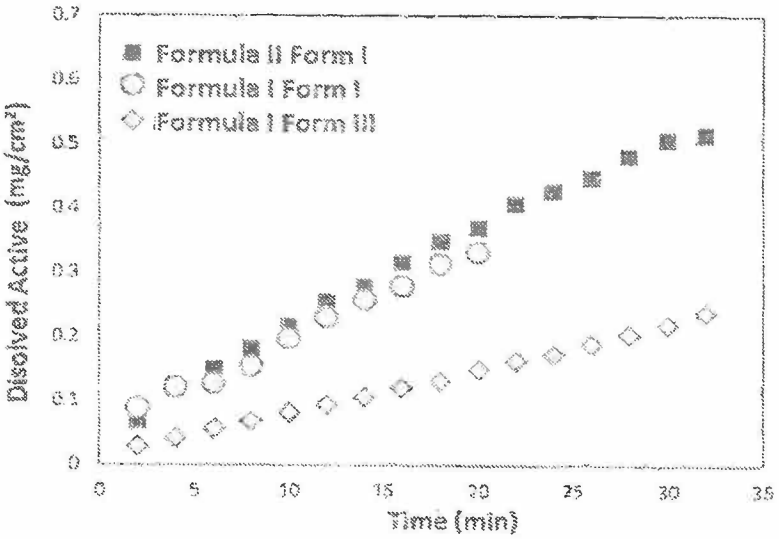


Figure 5

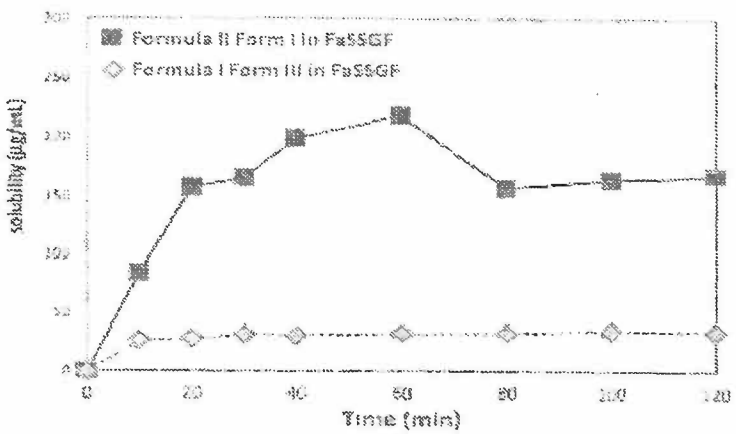


Figure 6

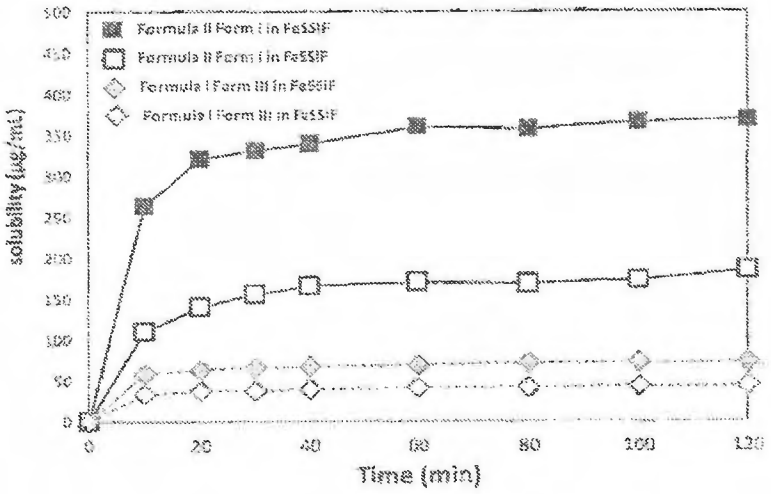

Formula II Form I in FeSSIF
Formula II Form I in FeSSIF
Formula I Form III in FeSSIF
Formula I Form III in FeSSIF
solubility (µg/mL)
500
450
400
350
300
250
200
150
100
50
0
0
20
40
60
80
100
120
Time (min)

Figure 7

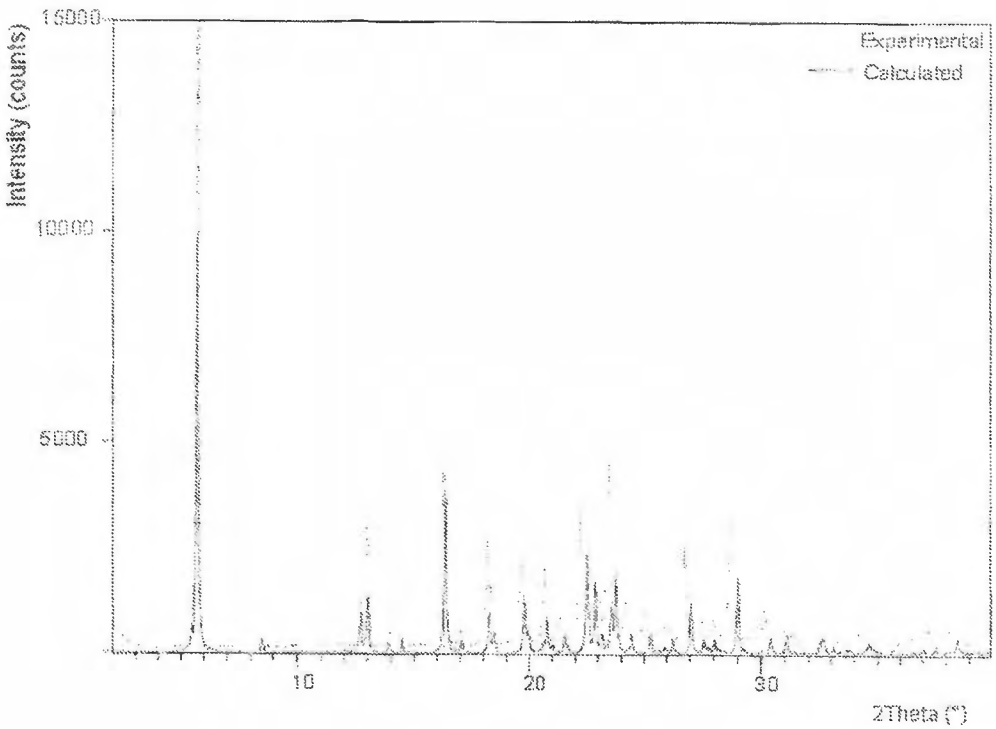

15000
10000
5000
Intensity (counts)
Experimental
Calculated
10
20
30
2Theta (°)

Figure 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/036757

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/14 A61K31/535 A61P31/18
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 2014/100323 A1 (GILEAD SCIENCES INC [US]) 26 June 2014 (2014-06-26) cited in the application example 42 claim 32	1-25
A	EP 2 465 580 A1 (GLAXOSMITHKLINE LLC [US]; SHIONOGI & CO [JP]) 20 June 2012 (2012-06-20) claims 1-6	1-25

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 August 2015	09/09/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Götz, Gerhard

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/036757

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		VN 34404 A1	25-07-2013
		WO 2006116764 A1	02-11-2006

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1 February 2013 (01.02.2013)

(25) Filing Language: English

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(30) Priority Data:

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61/624,676	16 April 2012 (16.04.2012)	US
61/692,392	23 August 2012 (23.08.2012)	US
61/737,493	14 December 2012 (14.12.2012)	US

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(72) Inventor: **RAMANATHAN, Srinivasan**; 300 De Anza, San Carlos, CA 94070 (US).

(74) Agents: **PERRY, Lawrence, S.** et al.; Fitzpatrick, Cella, Harper & Scinto, 1290 Avenue of the Americas, New York, NY 10104-3800 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2013/116720 A1

(54) Title: COMBINATION THERAPY COMPRISING TENOFOVIR ALAFENAMIDE HEMIFUMARATE AND COBICISTAT FOR USE IN THE TREATMENT OF VIRAL INFECTIONS

(57) Abstract: The use of the hemifumarate form of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} (tenofovir alafenamide hemifumarate) in combination with cobicistat is disclosed. In addition, the combination of tenofovir alafenamide hemifumarate, cobicistat, emtricitabine, and elvitegravir, and the combination of tenofovir alafenamide hemifumarate, cobicistat, emtricitabine, and darunavir, are disclosed.

TITLE

COMBINATION THERAPY COMPRISING TENOFOVIR ALAFENAMIDE HEMIFUMARATE AND COBICISTAT FOR USE IN THE TREATMENT OF VIRAL INFECTIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority from U.S. Provisional Patent Application No. 61/594,894, filed February 3, 2012; U.S. Provisional Patent Application No. 61/618,411, filed March 30, 2012; U.S. Provisional Patent Application No. 61/624,676, filed April 16, 2012; U.S. Provisional Patent Application No. 61/692,392, filed August 23, 2012; and U.S. Provisional Patent Application No. 61/737,493, filed December 14, 2012, the content of each of which is hereby incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

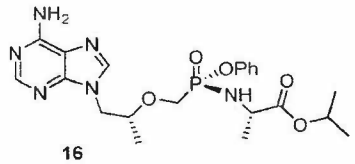
Field of the Invention

[0002] Tenofovir {9-R-[(2-phosphonomethoxy)propyl]adenine}, an acyclic nucleotide analog of dAMP, is a potent *in vitro* and *in vivo* inhibitor of human immunodeficiency virus type 1 (HIV-1) replication. Tenofovir is sequentially phosphorylated in the cell by AMP kinase and nucleoside diphosphate kinase to the active species, tenofovir diphosphate, which acts as a competitive inhibitor of HIV-1 reverse transcriptase that terminates the growing viral DNA chain. The presence of a nonhydrolyzable phosphonic acid moiety in tenofovir circumvents an

initial phosphorylation step that can be rate limiting for the activation of nucleoside analog inhibitors of HIV reverse transcriptase. Due to the presence of a phosphonate group, tenofovir is negatively charged at neutral pH, thus limiting its oral bioavailability.

[0003] Tenofovir disoproxil fumarate (TDF; VIREAD®), the first generation oral prodrug of tenofovir, has been extensively studied in clinical trials and has received marketing authorization in many countries as a once-daily tablet (300 mg) in combination with other antiretroviral agents for the treatment of HIV-1 infection.

[0004] U.S. Patent No. 7,390,791 describes certain prodrugs of phosphonate nucleotide analogs that are useful in therapy. One such prodrug is 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]-methoxy]propyl]adenine **16**:



16

[0005] GS-7340 {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} is an isopropylalaninyl phenyl ester prodrug of tenofovir (9-[(2-phosphonomethoxy) propyl]adenine). GS-7340 exhibits potent anti-HIV activity 500- to 1000-fold enhanced activity relative to tenofovir against HIV-1 in T cells, activated peripheral blood mononuclear lymphocytes (PBMCs), and macrophages. GS-7340 also has enhanced ability to deliver and increase the accumulation of the parent tenofovir into PBMCs and other lymphatic tissues *in vivo*. It is also a potent inhibitor of hepatitis B virus.

[0006] GS-7340 is metabolized to tenofovir, which is not dependent on an intracellular nucleoside kinase activity for the first step in the conversion to the active metabolite, tenofovir diphosphate (PMPApp). The cellular enzymes responsible for tenofovir metabolism to the active diphosphorylated form are

adenylate kinase and nucleotide diphosphate kinase, which are highly active and ubiquitous. Adenylate kinase exists as multiple isozymes (AK1 to AK4), with the phosphorylation of tenofovir mediated most efficiently by AK2.

[0007] Tenofovir does not interact significantly with human drug metabolizing cytochrome P450 enzymes or UDP-glucuronosyltransferases as a substrate, inhibitor, or inducer, *in vitro* or *in vivo* in humans. GS-7340 has limited potential to alter cytochrome P450 enzyme activity through inhibition ($IC_{50} > 7\mu M$ compared to all isoforms tested). Similarly GS-7340 does not inhibit UGT1A1 function at concentrations up to 50 μM. In addition, GS-7340 is not an activator of either the aryl hydrocarbon receptor or human pregnane X receptor.

[0008] Although tenofovir and GS-7340 show desirable activities, the treatment cost and the potential for unwanted side effects can both increase as the required dose of a drug increases. Therefore, there is a need for methods and compositions that are useful for achieving an acceptable anti-viral effect using a reduced dose of tenofovir or GS-7340.

[0009] Along with U.S. Patent No. 7,390,791, U.S. Patent No. 7,803,788 (the content of each of which is incorporated by reference herein in its entirety) also describes certain prodrugs of phosphonate nucleotide analogs that are useful in therapy. As noted above, one such prodrug is 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine. This compound is also known by the Chemical Abstract name L-alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester. U.S. Patent Nos. 7,390,791 and 7,803,788 disclose a monofumarate form of this compound and its preparation method (see, e.g., Example 4).

SUMMARY OF THE INVENTION

[0010] It has been determined that the systemic exposure to GS-7340 in humans improves when GS-7340 is administered with cobicistat (1,3-thiazol-5-ylmethyl (2R,5R)-(5-{[(2S)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]]-4-(morpholin-4-yl)butanamido}-1,6-diphenylhexan-

2-yl)carbamate). When administered with cobicistat, GS-7340 was calculated to have a systemic exposure equivalent 2.2 fold higher than a dose of GS-7340 alone. In another case, GS-7340 administered with cobicistat was calculated to have a systemic exposure equivalent 3-4 fold higher than a dose of GS-7340 alone. In another case, GS-7340 administered with cobicistat was calculated to have a systemic exposure equivalent 1.3 fold higher than a dose of GS-7340 alone.

[0011] In one embodiment, the invention provides for the use of the compound GS-7340 or a pharmaceutically acceptable salt thereof and cobicistat, or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a viral infection in a human. The cobicistat may be coadministered with GS-7340. GS-7340 or a pharmaceutically acceptable salt thereof, may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg, or other ranges as set forth below. Cobicistat or a pharmaceutically acceptable salt thereof may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. GS-7340, or a pharmaceutically acceptable salt thereof, and cobicistat or a pharmaceutically acceptable salt thereof, may be coadministered. A unit dosage form comprising a daily amount of GS-7340 or a pharmaceutically acceptable salt thereof, and a daily amount of cobicistat or pharmaceutically acceptable salt thereof, may be used. The virus of the viral infection may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0012] In one embodiment, the invention provides for the use of the compound GS-7340, or a pharmaceutically acceptable salt thereof, and cobicistat, or a pharmaceutically acceptable salt thereof, for improving the pharmacokinetics of GS-7340. The cobicistat may be coadministered with GS-7340. GS-7340, or a pharmaceutically acceptable salt thereof, may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg, or other ranges as set forth below. Cobicistat or a pharmaceutically acceptable salt thereof may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. GS-7340, or a pharmaceutically acceptable salt thereof, and the cobicistat or pharmaceutically acceptable salt thereof may be coadministered. A unit dosage form comprising a daily amount GS-7340 or a pharmaceutically acceptable salt thereof, and a daily amount cobicistat or pharmaceutically acceptable salt thereof may be used. The

use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0013] In one embodiment, the invention provides for the use of the compound GS-7340 or a pharmaceutically acceptable salt thereof and cobicistat, or a pharmaceutically acceptable salt thereof, for improving the C_{max} of GS-7340. The cobicistat may be coadministered with GS-7340. GS-7340 or a pharmaceutically acceptable salt thereof, may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat or a pharmaceutically acceptable salt thereof may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. GS-7340, or a pharmaceutically acceptable salt thereof, and the cobicistat or pharmaceutically acceptable salt thereof may be coadministered. A unit dosage form comprising a daily amount of GS-7340 or a pharmaceutically acceptable salt thereof, and a daily amount of cobicistat or pharmaceutically acceptable salt thereof may be used. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0014] In one embodiment, the invention provides for the use of the compound GS-7340 or a pharmaceutically acceptable salt thereof and cobicistat, or a pharmaceutically acceptable salt thereof, for improving blood levels of GS-7340. The cobicistat may be coadministered with GS-7340. GS-7340 or a pharmaceutically acceptable salt thereof, may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat or a pharmaceutically acceptable salt thereof may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. GS-7340, or a pharmaceutically acceptable salt thereof, and the cobicistat or pharmaceutically acceptable salt thereof may be coadministered. A unit dosage form comprising a daily amount GS-7340 or a pharmaceutically acceptable salt thereof, and a daily amount cobicistat or pharmaceutically acceptable salt thereof may be used. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0015] In one embodiment, the invention provides for a composition comprising a unit-dosage form of GS-7340 or a pharmaceutically acceptable salt thereof; a unit-dosage form of cobicistat, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent. The composition may include GS-7340 or a pharmaceutically acceptable salt thereof in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. The composition may include cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. The unit dosage form may be a single daily dosage.

[0016] In one embodiment, the invention provides for a kit comprising: (1) GS-7340, or a pharmaceutically acceptable salt thereof; (2) cobicistat, or a pharmaceutically acceptable salt thereof; (3) one or more containers; and (4) prescribing information regarding administering the GS-7340 or a pharmaceutically acceptable salt thereof with the cobicistat or the pharmaceutically acceptable salt thereof. The kit may include GS-7340 or a pharmaceutically acceptable salt thereof in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. The kit may include cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg.

[0017] In one embodiment, the invention provides for a method of treating a viral infection in a human comprising coadministering GS-7340 with cobicistat, or a pharmaceutically acceptable salt thereof, wherein the dose of cobicistat coadministered with the GS-7340 provides a systemic exposure of GS-7340 comparable to the systemic exposure obtainable by administration of a greater dose of GS-7340 in the absence of cobicistat. GS-7340 or a pharmaceutically acceptable salt thereof in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below may be coadministered with cobicistat. Cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg may be coadministered with GS-7340. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0018] In one embodiment, the invention provides for a method for inhibiting activity of a retroviral reverse transcriptase in a human comprising coadministering GS-7340 with cobicistat, or a pharmaceutically acceptable salt thereof, wherein the dose of cobicistat coadministered with the GS-7340 provides a systemic exposure

of GS-7340 comparable to the systemic exposure obtainable by administration of a greater dose of GS-7340 in the absence of cobicistat. GS-7340 or a pharmaceutically acceptable salt thereof in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below may be coadministered with cobicistat. Cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg may be coadministered with GS-7340. The virus may be human immunodeficiency virus (HIV).

[0019] In one embodiment, the invention provides for the use of the compound GS-7340 or a pharmaceutically acceptable salt thereof coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a viral infection. The invention further provides for the use of the compound GS-7340 or a pharmaceutically acceptable salt thereof coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a viral infection in a human. GS-7340 or a pharmaceutically acceptable salt thereof may be used in a subtherapeutic amount (or, in some embodiments throughout, in a therapeutic amount). GS-7340 or a pharmaceutically acceptable salt thereof may be used in amounts of 3 mg, 8 + 3 mg, 10 + 5 mg, 25 + 5 mg, or 40 + 10 mg or other ranges as set forth below. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Cobicistat may be used in an amount that provides a systemic exposure of GS-7340 comparable to the systemic exposure obtainable by administration of a greater dose of GS-7340 in the absence of cobicistat is used in the manufacture of the medicament. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0020] In one embodiment, the invention provides for the use of the compound GS-7340 or a pharmaceutically acceptable salt thereof coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase. The invention further provides for the use of the compound GS-7340 or a pharmaceutically acceptable salt thereof coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase in a human. GS-7340 or a

pharmaceutically acceptable salt thereof may be used in a subtherapeutic amount. GS-7340 or a pharmaceutically acceptable salt thereof may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. The cobicistat may be used in an amount that provides a systemic exposure of GS-7340 comparable to the systemic exposure obtainable by administration of a greater dose of GS-7340 in the absence of cobicistat is used in the manufacture of the medicament. The virus may be human immunodeficiency virus (HIV).

[0021] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament useful for improving the pharmacokinetics of GS-7340, or a pharmaceutically acceptable salt thereof, following administration to a human. GS-7340 or a pharmaceutically acceptable salt thereof may be used in a subtherapeutic amount. GS-7340 or a pharmaceutically acceptable salt thereof may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. The cobicistat may be used in an amount that provides a systemic exposure of GS-7340 comparable to the systemic exposure obtainable by administration of a greater dose of GS-7340 in the absence of cobicistat is used in the manufacture of the medicament. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0022] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament useful for improving the pharmacokinetics of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine}, or a pharmaceutically acceptable salt thereof, following administration to a human. GS-7340 or a pharmaceutically acceptable salt thereof may be used in a subtherapeutic amount. {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine}, or a pharmaceutically acceptable salt thereof, may be used in amounts of 3 mg,

8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth herein. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. The cobicistat may be used in an amount that provides a systemic exposure of GS-7340 comparable to the systemic exposure obtainable by administration of a greater dose of GS-7340 in the absence of cobicistat is used in the manufacture of the medicament. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0023] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of GS-7340 by about 30-70%, or a pharmaceutically acceptable salt thereof, upon administration of the cobicistat. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0024] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of GS-7340 by about 2-4 fold, or a pharmaceutically acceptable salt thereof, upon administration of the cobicistat. In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of GS-7340 by about 3 fold, or a pharmaceutically acceptable salt thereof, upon administration of the cobicistat. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0025] In one embodiment, the invention provides for a method of treating a viral infection in a human comprising coadministering 1) GS-7340 or a pharmaceutically acceptable salt thereof; and 2) cobicistat, or a pharmaceutically acceptable salt thereof to the human. GS-7340 or a pharmaceutically acceptable salt thereof is administered in a subtherapeutic amount. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0026] In one embodiment, the invention provides for a use of a subtherapeutic dose of GS-7340 coadministered with cobicistat for treating a viral infection. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0027] In one embodiment, the invention provides for the use of a subtherapeutic dose of GS-7340 coadministered with cobicistat for inhibiting retroviral reverse transcriptase. The virus may be human immunodeficiency virus (HIV).

[0028] In one embodiment, the invention provides for an anti-virus agent(s) comprising (a) a compound GS-7340 or a pharmaceutically acceptable salt thereof and (b) cobicistat, or a pharmaceutically acceptable salt thereof. The anti-virus agent(s) may include GS-7340 or a pharmaceutically acceptable salt thereof may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. The anti-virus agent(s) may include cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. The cobicistat may be used in an amount that provides a systemic exposure of GS-7340 comparable to the systemic exposure obtainable by administration of a greater dose of GS-7340 in the absence of cobicistat is used in the manufacture of the medicament. The anti-virus agent may further include 200 mg of emtricitabine and 150 mg of elvitegravir. The anti-virus agent may further include 150 mg cobicistat, 8 or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may further include 150 mg cobicistat, 25or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may further include 150 mg cobicistat, 10 or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may include 150 mg cobicistat, 8 mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may include 150 mg cobicistat, 10 mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine.

[0029] In one embodiment, the invention provides for a unit-dosage of GS-7340 or a pharmaceutically acceptable salt thereof and cobicistat, or a pharmaceutically acceptable salt thereof, wherein the unit-dosage is a daily dose. GS-7340 may be present in a subtherapeutic amount. The unit-dosage may further include 150 mg cobicistat, 8 or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine. The unit-dosage may further include 150 mg cobicistat, 25or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine. The unit-dosage may further

include 150 mg cobicistat, 10 or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine. The unit-dosage may include 150 mg cobicistat, 10 mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine.

[0030] In one embodiment, the invention provides the use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament useful for improving the pharmacokinetics of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine}, or a pharmaceutically acceptable salt thereof, following administration to a human. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be, e.g., human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0031] In one embodiment, the invention provides cobicistat for use in improving the pharmacokinetics of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or a pharmaceutically acceptable salt thereof, following administration to a human. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0032] In one embodiment, the invention provides a kit comprising: (1) {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine}, or a pharmaceutically acceptable salt thereof; (2) cobicistat, or a pharmaceutically acceptable salt thereof; (3) one or more containers; and (4) prescribing information regarding administering the {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or a pharmaceutically acceptable salt thereof with the cobicistat or a pharmaceutically acceptable salt thereof.

[0033] In one embodiment, the invention provides a kit comprising: (1) a unit dosage form comprising 5-100 mg of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine}, or a pharmaceutically acceptable salt thereof; (2) a unit dosage form comprising 150 mg cobicistat, or a pharmaceutically acceptable salt thereof; (3) one or more

containers; and (4) prescribing information regarding administering the {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or a pharmaceutically acceptable salt thereof with cobicistat or a pharmaceutically acceptable salt thereof.

[0034] In one embodiment, the invention provides a use of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or its pharmaceutically acceptable salt for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase in a human, comprising administering GS-7340 or a pharmaceutically acceptable salt thereof, and cobicistat, or a pharmaceutically acceptable salt thereof to the human. The virus may be human immunodeficiency virus (HIV).

[0035] In one embodiment, the invention provides {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or its pharmaceutically acceptable salt; and cobicistat, or a pharmaceutically acceptable salt thereof; for use in inhibiting activity of a retroviral reverse transcriptase in a human.

[0036] In one embodiment, the invention provides a use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament for a human useful for reducing a dose between about 30-70% of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or a pharmaceutically acceptable salt thereof, upon administration of the cobicistat. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0037] In one embodiment, the invention provides the use of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or a pharmaceutically acceptable salt thereof; and cobicistat or a pharmaceutically acceptable salt thereof for the prophylactic or therapeutic treatment of a viral infection in a human. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0038] In one embodiment, the invention provides an anti-viral agent(s) comprising (a) {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or a pharmaceutically acceptable salt thereof, which is used in combination with (b) cobicistat or a pharmaceutically acceptable salt thereof for use in the prophylactic or therapeutic treatment of a viral infection in a human.

[0039] It has also been determined that the systemic exposure to tenofovir in humans improves when tenofovir is administered with cobicistat. When administered with cobicistat, tenofovir was calculated to have a systemic exposure equivalent 3 to 4 fold higher than a dose of tenofovir alone.

[0040] In one embodiment, the invention provides for the use of the compound tenofovir or a pharmaceutically acceptable salt thereof and cobicistat, or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a viral infection in a human. Tenofovir may be used in amounts of less than 300 mg, 200 mg or less and 100 mg or less. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg, and 150 mg. The tenofovir or a pharmaceutically acceptable salt thereof, and the cobicistat or pharmaceutically acceptable salt thereof may be coadministered. The use may provide a unit dosage form comprising a daily amount tenofovir or a pharmaceutically acceptable salt thereof, and a daily amount cobicistat or pharmaceutically acceptable salt thereof is administered. The virus may be human immunodeficiency virus (HIV).

[0041] In one embodiment, the invention provides for a composition comprising a unit-dosage form of tenofovir or a pharmaceutically acceptable salt thereof; a unit-dosage form of cobicistat, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent. Tenofovir may be present in the composition in amounts of less than 300 mg, 200 mg or less and 100 mg or less. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg, and 150 mg.

[0042] In one embodiment, the invention provides for a kit that includes (1) tenofovir, or a pharmaceutically acceptable salt thereof; (2) cobicistat, or a pharmaceutically acceptable salt thereof; (3) one or more containers; and (4) prescribing information regarding administering the tenofovir or a

pharmaceutically acceptable salt thereof with the cobicistat or the pharmaceutically acceptable salt thereof. Tenofovir may be present in the kit in amounts of less than 300 mg, 200 mg or less and 100 mg or less. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg, and 150 mg.

[0043] In one embodiment, the invention provides for a method of treating a viral infection in a human that includes coadministering tenofovir with cobicistat, or a pharmaceutically acceptable salt thereof, wherein the dose of cobicistat coadministered with the tenofovir provides a systemic exposure of tenofovir comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir in the absence of cobicistat. Tenofovir may be administered in amounts of less than 300 mg, 200 mg or less and 100 mg or less. Cobicistat may be administered in amounts of 50-500 mg, 100-400 mg, 100-300 mg, and 150 mg. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0044] In one embodiment, the invention provides for a method for inhibiting activity of a retroviral reverse transcriptase in a human comprising coadministering tenofovir with cobicistat, or a pharmaceutically acceptable salt thereof, wherein the dose of tenofovir coadministered with the cobicistat provides a systemic exposure of tenofovir comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir in the absence of cobicistat. Tenofovir may be coadministered in amounts of less than 300 mg, 200 mg or less and 100 mg or less. Cobicistat may be coadministered in amounts of 50-500 mg, 100-400 mg, 100-300 mg, and 150 mg. The virus may be human immunodeficiency virus (HIV)

[0045] In one embodiment, the invention provides for the use of the compound tenofovir or a pharmaceutically acceptable salt thereof coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a viral infection. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0046] In one embodiment, the invention provides for the use of the compound tenofovir or a pharmaceutically acceptable salt thereof coadministered with

cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a viral infection in a human. The tenofovir or a pharmaceutically acceptable salt thereof may be used in a subtherapeutic amount (or, in some embodiments throughout, in a therapeutic amount). Tenofovir may be administered in amounts of less than 300 mg, 200 mg or less and 100 mg or less. The cobicistat may be administered in an amount that provides a systemic exposure of tenofovir comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir in the absence of cobicistat is used in the manufacture of the medicament. Cobicistat in an amount of 150 mg may be used in the manufacture of the medicament. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0047] In one embodiment, the invention provides for the use of the compound tenofovir or a pharmaceutically acceptable salt thereof coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0048] In one embodiment, the invention provides for use of the compound tenofovir or a pharmaceutically acceptable salt thereof coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase in a human. The tenofovir or a pharmaceutically acceptable salt thereof may be used in a subtherapeutic amount. Tenofovir may be used in amounts of less than 300 mg, 200 mg or less and 100 mg or less. The cobicistat may be coadministered in an amount that provides a systemic exposure of tenofovir comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir in the absence of cobicistat is used in the manufacture of the medicament. Cobicistat in an amount of 150 mg may be coadministered. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0049] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament useful for improving the pharmacokinetics of tenofovir, or a pharmaceutically acceptable salt thereof, following administration to a human. The tenofovir or a pharmaceutically acceptable salt thereof may be used in a subtherapeutic amount. Tenofovir or a pharmaceutically acceptable salt thereof, may be coadministered to the human in an amount of 100 mg or less, 200 mg or less or in amount less than 300 mg. Cobicistat may be used in an amount that provides a systemic exposure of tenofovir comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir in the absence of cobicistat is used in the manufacture of the medicament. Cobicistat in an amount 150 mg may be used to prepare the medicament. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0050] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of tenofovir by about 30-70%, or a pharmaceutically acceptable salt thereof, upon administration of the cobicistat. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0051] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of tenofovir by about 2 to 4 fold, or a pharmaceutically acceptable salt thereof, upon administration of the cobicistat. In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of tenofovir by about 3-fold, or a pharmaceutically acceptable salt thereof, upon administration of the cobicistat. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0052] In one embodiment, the invention provides for a method of treating a viral infection in a human comprising coadministering 1) tenofovir or a pharmaceutically acceptable salt thereof; and 2) cobicistat, or a pharmaceutically acceptable salt thereof to the human. The tenofovir or a pharmaceutically acceptable salt thereof may be administered in a subtherapeutic amount. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0053] In one embodiment, the invention provides for a use of a subtherapeutic dose of tenofovir coadministered with cobicistat for treating a viral infection. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0054] In one embodiment, the invention provides for a use of a subtherapeutic dose of tenofovir coadministered with cobicistat for inhibiting retroviral reverse transcriptase. The virus may be human immunodeficiency virus (HIV).

[0055] In one embodiment, the invention provides for an anti-virus agent(s) comprising (a) a compound tenofovir or a pharmaceutically acceptable salt thereof and (b) cobicistat, or a pharmaceutically acceptable salt thereof. The tenofovir may be present in the anti-virus agent(s) in a subtherapeutic amount. The tenofovir may be present in the anti-virus agent(s) in an amount of 100 mg or less, 200 mg or less or less than 300 mg. The cobicistat coadministered with the tenofovir may be present in the anti-virus agent(s) in an amount that provides a systemic exposure of tenofovir comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir in the absence of cobicistat. The anti-virus agent may further include cobicistat in an amount of 150 mg. The anti-virus agent may further include 200 mg of emtricitabine and 150 mg of elvitegravir. The anti-virus agent may include 150 mg cobicistat, 100 or less mg tenofovir, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may include 150 mg cobicistat, 200 or less mg tenofovir, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may include 150 mg cobicistat, less than 300 mg tenofovir, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may include 150 mg cobicistat, 50 mg tenofovir, 150 mg elvitegravir, and 200 mg emtricitabine. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0056] In one embodiment, the invention provides for a unit-dosage of tenofovir or a pharmaceutically acceptable salt thereof and cobicistat, or a pharmaceutically acceptable salt thereof, wherein the unit-dosage is a daily dose. Tenofovir may be present in a subtherapeutic amount. The unit-dosage may include 100 mg or less, 200 mg or less or less than 300 mg of tenofovir. The unit-dosage may include an amount of cobicistat that provides a systemic exposure of tenofovir comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir in the absence of cobicistat. The unit-dosage may include 150 mg of cobicistat. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0057] Also described is a hemifumarate form of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine. The name for 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine (GS-7340) is tenofovir alafenamide. The hemifumarate form of tenofovir alafenamide is also referred to herein as tenofovir alafenamide hemifumarate.

[0058] In one embodiment of the invention is provided tenofovir alafenamide hemifumarate, especially in combination with cobicistat and/or with other an additional therapeutic agent or agents.

[0059] In another embodiment is provided tenofovir alafenamide hemifumarate, wherein the ratio of fumaric acid to tenofovir alafenamide is 0.5 ± 0.1, or 0.5 ± 0.05, or 0.5 ± 0.01, or about 0.5.

[0060] In one embodiment is provided tenofovir alafenamide hemifumarate in a solid form.

[0061] In one embodiment is provided tenofovir alafenamide hemifumarate that has an X-ray powder diffraction (XRPD) pattern having 2theta values of 6.9 ± 0.2° and 8.6 ± 0.2°. In another embodiment is provided tenofovir alafenamide hemifumarate wherein the XRPD pattern comprises 2theta values of 6.9 ± 0.2°, 8.6 + 0.2°, 11.0 + 0.2°, 15.9 + 0.2°, and 20.2 + 0.2°.

[0062] In one embodiment is provided tenofovir alafenamide hemifumarate that has a differential scanning calorimetry (DSC) onset endotherm of 131 ± 2 °C, or 131 ± 1 °C.

[0063] In one embodiment is provided a pharmaceutical composition comprising tenofovir alafenamide hemifumarate and a pharmaceutically acceptable excipient. In another embodiment is provided the pharmaceutical composition, further comprising an additional therapeutic agent. In a further embodiment, the additional therapeutic agent is selected from the group consisting of human immunodeficiency virus (HIV) protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, CCR5 inhibitors, and additional protease inhibiting compounds.

[0064] In one embodiment is provided a method for treating a human immunodeficiency virus (HIV) infection comprising administering to a subject in need thereof a therapeutically effective amount of tenofovir alafenamide hemifumarate. In another embodiment is provided a method for treating an HIV infection comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising tenofovir alafenamide hemifumarate. In a further embodiment, the method comprises administering to the subject one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, CCR5 inhibitors, and additional protease inhibiting compounds.

[0065] In one embodiment is provided a method for treating a hepatitis B virus (HBV) infection comprising administering to a subject in need thereof a therapeutically effective amount of tenofovir alafenamide hemifumarate. In another embodiment is provided a method for treating an HBV infection comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition comprising tenofovir alafenamide hemifumarate.

[0066] In one embodiment is provided a method for preparing a pharmaceutical composition comprising combining tenofovir alafenamide hemifumarate and a pharmaceutically acceptable excipient to provide the pharmaceutical composition.

[0067] In one embodiment is provided tenofovir alafenamide hemifumarate for use in medical therapy.

[0068] In one embodiment is provided the use of tenofovir alafenamide hemifumarate for the prophylactic or therapeutic treatment of an HIV infection. In another embodiment is provided the use of tenofovir alafenamide hemifumarate to treat an HIV infection. In a further embodiment is provided the use of tenofovir alafenamide hemifumarate for the preparation or manufacture of a medicament for the treatment of an HIV infection. In another further embodiment is provided tenofovir alafenamide hemifumarate for use in treating an HIV infection.

[0069] In one embodiment is provided the use of tenofovir alafenamide hemifumarate for the prophylactic or therapeutic treatment of an HBV infection. In another embodiment is provided the use of tenofovir alafenamide hemifumarate to treat an HBV infection. In a further embodiment is provided the use of tenofovir alafenamide hemifumarate for the preparation or manufacture of a medicament for the treatment of an HBV infection. In another further embodiment is provided tenofovir alafenamide hemifumarate for use in treating an HBV infection.

[0070] In some embodiments of the invention, the methods of treating and the like comprise administration of multiple daily doses. In other embodiments, the methods of treating and the like comprise administration of a single daily dose.

[0071] In one embodiment, the invention provides for the use of tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a viral infection in a human. The cobicistat may be coadministered with tenofovir alafenamide hemifumarate. Tenofovir alafenamide hemifumarate may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat or a pharmaceutically acceptable salt thereof may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Tenofovir alafenamide hemifumarate and cobicistat or pharmaceutically acceptable salt thereof may be coadministered. A unit dosage form comprising a daily amount of tenofovir alafenamide hemifumarate, and a daily amount of cobicistat or

pharmaceutically acceptable salt thereof may be used. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0072] In one embodiment, the invention provides for the use tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, for improving the pharmacokinetics of tenofovir alafenamide hemifumarate. Cobicistat may be coadministered with tenofovir alafenamide hemifumarate. Tenofovir alafenamide hemifumarate may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat or a pharmaceutically acceptable salt thereof may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Tenofovir alafenamide hemifumarate and cobicistat, or pharmaceutically acceptable salt thereof, may be coadministered. A unit dosage form comprising a daily amount of tenofovir alafenamide hemifumarate, and a daily amount of cobicistat or pharmaceutically acceptable salt thereof may be used. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0073] In one embodiment, the invention provides for the use of tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, for improving the C_{max} of tenofovir alafenamide hemifumarate. The cobicistat may be coadministered with tenofovir alafenamide hemifumarate. Tenofovir alafenamide hemifumarate may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat or a pharmaceutically acceptable salt thereof may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Tenofovir alafenamide hemifumarate and cobicistat, or pharmaceutically acceptable salt thereof, may be coadministered. A unit dosage form comprising a daily amount of tenofovir alafenamide hemifumarate, and a daily amount of cobicistat, or a pharmaceutically acceptable salt thereof, may be used. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0074] In one embodiment, the invention provides for the use of tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt

thereof, for improving blood levels of tenofovir alafenamide hemifumarate. The cobicistat may be coadministered with tenofovir alafenamide hemifumarate. Tenofovir alafenamide hemifumarate may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat, or a pharmaceutically acceptable salt thereof, may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, may be coadministered. A unit dosage form comprising a daily amount tenofovir alafenamide hemifumarate, and a daily amount cobicistat, or a pharmaceutically acceptable salt thereof, may be used. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0075] In one embodiment, the invention provides for a composition comprising a unit-dosage form of tenofovir alafenamide hemifumarate; a unit-dosage form of cobicistat, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent. The composition may include tenofovir alafenamide hemifumarate in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. The composition may include cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. The unit-dosage form may be a single daily dosage.

[0076] In one embodiment, the invention provides for a kit comprising: (1) tenofovir alafenamide hemifumarate; (2) cobicistat, or a pharmaceutically acceptable salt thereof; (3) one or more containers; and (4) prescribing information regarding administering the tenofovir alafenamide hemifumarate with the cobicistat, or the pharmaceutically acceptable salt thereof. The kit may include tenofovir alafenamide hemifumarate in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. The kit may include cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg.

[0077] In one embodiment, the invention provides for a method of treating a viral infection in a human comprising coadministering tenofovir alafenamide hemifumarate with cobicistat, or a pharmaceutically acceptable salt thereof, wherein the dose of cobicistat coadministered with the tenofovir alafenamide

hemifumarate provides a systemic exposure of tenofovir alafenamide hemifumarate comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir alafenamide hemifumarate in the absence of cobicistat. Tenofovir alafenamide hemifumarate in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below may be coadministered with cobicistat. Cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg may be coadministered with tenofovir alafenamide hemifumarate. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0078] In one embodiment, the invention provides for a method for inhibiting activity of a retroviral reverse transcriptase in a human comprising coadministering tenofovir alafenamide hemifumarate with cobicistat, or a pharmaceutically acceptable salt thereof, wherein the dose of cobicistat coadministered with the tenofovir alafenamide hemifumarate provides a systemic exposure of tenofovir alafenamide hemifumarate comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir alafenamide hemifumarate in the absence of cobicistat. Tenofovir alafenamide hemifumarate or a pharmaceutically acceptable salt thereof in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below may be coadministered with cobicistat. Cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg may be coadministered with tenofovir alafenamide hemifumarate. The virus may be human immunodeficiency virus (HIV).

[0079] In one embodiment, the invention provides for the use of tenofovir alafenamide hemifumarate coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a viral infection. The invention further provides for the use of tenofovir alafenamide hemifumarate coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a viral infection in a human. Tenofovir alafenamide hemifumarate may be used in a subtherapeutic amount (or, in some embodiments throughout, in a therapeutic amount). Tenofovir alafenamide hemifumarate may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Cobicistat

may be used in an amount that provides a systemic exposure of tenofovir alafenamide hemifumarate comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir alafenamide hemifumarate in the absence of cobicistat in the manufacture of the medicament. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0080] In one embodiment, the invention provides for the use of tenofovir alafenamide hemifumarate coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase. The invention further provides for the use of tenofovir alafenamide hemifumarate coadministered with cobicistat, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase in a human. Tenofovir alafenamide hemifumarate may be used in a subtherapeutic amount. Tenofovir alafenamide hemifumarate may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Cobicistat may be used in an amount that provides a systemic exposure of tenofovir alafenamide hemifumarate comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir alafenamide hemifumarate in the absence of cobicistat in the manufacture of the medicament. The virus may be human immunodeficiency virus (HIV).

[0081] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament useful for improving the pharmacokinetics of tenofovir alafenamide hemifumarate following administration to a human. Tenofovir alafenamide hemifumarate may be used in a subtherapeutic amount. Tenofovir alafenamide hemifumarate may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Cobicistat may be used in an amount that provides a systemic exposure of tenofovir alafenamide hemifumarate comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir alafenamide hemifumarate in the absence of cobicistat in the manufacture of the

medicament. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0082] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of tenofovir alafenamide hemifumarate by about 30-70% upon administration of the cobicistat. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0083] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of tenofovir alafenamide hemifumarate by about 2-4 fold upon administration of the cobicistat. In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of tenofovir alafenamide hemifumarate by about 3 fold upon administration of the cobicistat. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0084] In one embodiment, the invention provides for a method of treating a viral infection in a human comprising coadministering 1) tenofovir alafenamide hemifumarate; and 2) cobicistat, or a pharmaceutically acceptable salt thereof, to the human. Tenofovir alafenamide hemifumarate is administered in a subtherapeutic amount. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0085] In one embodiment, the invention provides for a use of a subtherapeutic dose of tenofovir alafenamide hemifumarate coadministered with cobicistat for treating a viral infection. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0086] In one embodiment, the invention provides for the use of a subtherapeutic dose of tenofovir alafenamide hemifumarate coadministered with cobicistat for

inhibiting retroviral reverse transcriptase. The virus may be human immunodeficiency virus (HIV)

[0087] In one embodiment, the invention provides for an anti-virus agent(s) comprising (a) tenofovir alafenamide hemifumarate and (b) cobicistat, or a pharmaceutically acceptable salt thereof. The anti-virus agent(s) may include tenofovir alafenamide hemifumarate in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. The anti-virus agent(s) may include cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. The cobicistat may be used in an amount that provides a systemic exposure of tenofovir alafenamide hemifumarate comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir alafenamide hemifumarate in the absence of cobicistat in the manufacture of the medicament. The anti-virus agent may further include 200 mg of emtricitabine and 150 mg of elvitegravir. The anti-virus agent may further include 150 mg cobicistat, 8 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may further include 150 mg cobicistat, 25 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may further include 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may include 150 mg cobicistat, 8 mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may include 150 mg cobicistat, 10 mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine.

[0088] In one embodiment, the invention provides for a unit-dosage of tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, wherein the unit-dosage is a daily dose. Tenofovir alafenamide hemifumarate may be present in a subtherapeutic amount. The unit-dosage may further include 150 mg cobicistat, 8 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine. The unit-dosage may further include 150 mg cobicistat, 25or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine. The unit-dosage

may further include 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine. The unit-dosage may include 150 mg cobicistat, 10 mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine.

[0089] In one embodiment, the invention provides the use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament useful for improving the pharmacokinetics of tenofovir alafenamide hemifumarate following administration to a human. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0090] In one embodiment, the invention provides cobicistat for use in improving the pharmacokinetics of tenofovir alafenamide hemifumarate following administration to a human. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0091] In one embodiment, the invention provides a kit comprising: (1) tenofovir alafenamide hemifumarate; (2) cobicistat, or a pharmaceutically acceptable salt thereof; (3) one or more containers; and (4) prescribing information regarding administering the tenofovir alafenamide hemifumarate with the cobicistat or a pharmaceutically acceptable salt thereof.

[0092] In one embodiment, the invention provides a kit comprising: (1) a unit dosage form comprising 5-100 mg of tenofovir alafenamide hemifumarate; (2) a unit dosage form comprising 150 mg cobicistat, or a pharmaceutically acceptable salt thereof; (3) one or more containers; and (4) prescribing information regarding administering the tenofovir alafenamide hemifumarate with cobicistat or a pharmaceutically acceptable salt thereof.

[0093] In one embodiment, the invention provides a use of tenofovir alafenamide hemifumarate for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase in a human, comprising administering tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, to the human. The virus may be human immunodeficiency virus (HIV).

[0094] In one embodiment, the invention provides tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, for use in inhibiting activity of a retroviral reverse transcriptase in a human.

[0095] In one embodiment, the invention provides a use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament for a human useful for reducing a dose between about 30-70% of tenofovir alafenamide hemifumarate upon administration of the cobicistat. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0096] In one embodiment, the invention provides the use of tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a viral infection in a human. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0097] In one embodiment, the invention provides an anti-viral agent(s) comprising (a) tenofovir alafenamide hemifumarate, which is used in combination with (b) cobicistat, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of a viral infection in a human.

[0098] In one embodiment, the invention provides for the use of ritonavir in the compositions, kits, unit-dosages and uses set forth above in place of cobicistat.

[0099] In one embodiment, the invention provides a method for inhibiting Pgp-mediated intestinal secretion of GS-7340, or a pharmaceutically acceptable salt thereof, in a human by coadministration of cobicistat, or a pharmaceutically acceptable salt thereof, with GS-7340, or a pharmaceutically acceptable salt thereof. In one embodiment, 150 mg of cobicistat, or a pharmaceutically acceptable salt thereof, is coadministered with 10 mg of GS-7340, or a pharmaceutically acceptable salt thereof.

[0100] In one embodiment, the invention provides a method for inhibiting Pgp-mediated intestinal secretion of tenofovir alafenamide hemifumarate in a human by coadministration of cobicistat, or a pharmaceutically acceptable salt thereof, with tenofovir alafenamide hemifumarate. In one embodiment, 150 mg of

cobicistat, or a pharmaceutically acceptable salt thereof, is coadministered with 10 mg of tenofovir alafenamide hemifumarate.

[0101] In one embodiment, the invention provides the use of an anti-virus agent for the prophylactic or therapeutic treatment of a viral infection in a human, wherein the anti-virus agent comprises 150 mg cobicistat, 10 or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine.

[0102] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering 150 mg cobicistat, 10 or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine to the human.

[0103] In one embodiment, the invention provides the use of 150 mg cobicistat, 10 or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine for the manufacture of a medicament for treating a viral infection in a human.

[0104] In one embodiment, the invention provides the use of an anti-virus agent for the prophylactic or therapeutic treatment of a viral infection in a human, wherein the anti-virus agent comprises 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine.

[0105] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine to the human.

[0106] In one embodiment, the invention provides the use of 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine for the manufacture of a medicament for treating a viral infection in a human.

[0107] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) tenofovir alafenamide hemifumarate, (b) cobicistat, or a pharmaceutically acceptable salt thereof, (c) emtricitabine, and (d) darunavir.

[0108] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) 8 or less mg of tenofovir alafenamide hemifumarate, (b) 150 mg of cobicistat, or a pharmaceutically acceptable salt thereof, (c) 200 mg of emtricitabine, and (d) 800 mg of darunavir.

[0109] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) 25 or less mg of tenofovir alafenamide hemifumarate, (b) 150 mg of cobicistat, or a pharmaceutically acceptable salt thereof, (c) 200 mg of emtricitabine, and (d) 800 mg of darunavir.

[0110] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) 10 mg of tenofovir alafenamide hemifumarate, (b) 150 mg of cobicistat, or a pharmaceutically acceptable salt thereof, (c) 200 mg of emtricitabine, and (d) 800 mg of darunavir.

[0111] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) GS-7340, or a pharmaceutically acceptable salt thereof, (b) cobicistat, or a pharmaceutically acceptable salt thereof, (c) emtricitabine, and (d) darunavir.

[0112] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) 8 or less mg of GS-7340, or a pharmaceutically acceptable salt thereof, (b) 150 mg of cobicistat, or a pharmaceutically acceptable salt thereof, (c) 200 mg of emtricitabine, and (d) 800 mg of darunavir.

[0113] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) 25 or less mg of GS-7340, or a pharmaceutically acceptable salt thereof, (b) 150 mg of cobicistat, or a pharmaceutically acceptable salt thereof, (c) 200 mg of emtricitabine, and (d) 800 mg of darunavir.

[0114] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) 10 mg of GS-7340, or a pharmaceutically acceptable salt thereof, (b) 150 mg of cobicistat, or a pharmaceutically acceptable salt thereof, (c) 200 mg of emtricitabine, and (d) 800 mg of darunavir.

[0115] In one embodiment, the invention provides the use of an anti-virus agent for the prophylactic or therapeutic treatment of a viral infection in a human, wherein the anti-virus agent comprises 150 mg cobicistat, 10 or less mg GS-7340, 800 mg of darunavir, and 200 mg emtricitabine.

[0116] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering 150 mg cobicistat, 10 or less mg GS-7340, 800 mg of darunavir, and 200 mg emtricitabine to the human.

[0117] In one embodiment, the invention provides the use of 150 mg cobicistat, 10 or less mg GS-7340, 800 mg of darunavir, and 200 mg emtricitabine for the manufacture of a medicament for treating a viral infection in a human.

[0118] In one embodiment, the invention provides the use of an anti-virus agent for the prophylactic or therapeutic treatment of a viral infection in a human, wherein the anti-virus agent comprises 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 800 mg of darunavir, and 200 mg emtricitabine.

[0119] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 800 mg of darunavir, and 200 mg emtricitabine to the human.

[0120] In one embodiment, the invention provides the use of 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 800 mg of darunavir, and 200 mg emtricitabine for the manufacture of a medicament for treating a viral infection in a human.

[0121] In one embodiment, the invention provides the use of a dose of a cytochrome p450 inhibitor, or a pharmaceutically acceptable salt thereof, to boost a dose GS-7340, or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a viral infection in a human. In one embodiment, the cytochrome p450 inhibitor is cobicistat, or a pharmaceutically acceptable salt thereof. In one further embodiment, the dose of GS-7340 would be a subtherapeutic amount absent the dose of cobicistat.

[0122] In one embodiment, the invention provides a composition comprising: a unit-dosage form of GS-7340, or a pharmaceutically acceptable salt thereof; a unit-dosage form of cobicistat, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent, wherein the amount of GS-7340 in the unit-dosage form is a subtherapeutic amount.

[0123] In one embodiment, the invention provides the use of a dose of a cytochrome p450 inhibitor, or a pharmaceutically acceptable salt thereof, to boost a dose tenofovir alafenamide hemifumarate for the prophylactic or therapeutic treatment of a viral infection in a human. In one embodiment, the cytochrome p450 inhibitor is cobicistat, or a pharmaceutically acceptable salt thereof. In one

further embodiment, the dose of tenofovir alafenamide hemifumarate would be a subtherapeutic amount absent the dose of cobicistat.

[0124] In one embodiment, the invention provides a composition comprising: a unit-dosage form of tenofovir alafenamide hemifumarate; a unit-dosage form of cobicistat, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent, wherein the amount of tenofovir alafenamide hemifumarate in the unit-dosage form is a subtherapeutic amount.

[0125] In one embodiment, the invention provides the uses and methods related to treating a viral infection, as noted herein, wherein the viral infection is human immunodeficiency virus (HIV).

[0126] In one embodiment, the invention provides the uses and methods related to treating a viral infection, as noted herein, wherein the viral infection is Hepatitis B virus (HBV).

[0127] In one embodiment, the invention provides a method of treating a viral infection in a human, comprising administering to the human a composition comprising cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, wherein the composition contains an amount of cobicistat, or a pharmaceutically acceptable salt thereof, sufficient for an amount of tenofovir alafenamide hemifumarate in the composition to provide an effect on the viral infection that is greater than the effect of the amount of tenofovir alafenamide hemifumarate in the absence of cobicistat, or a pharmaceutically acceptable salt thereof, and wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0128] In one embodiment, the invention provides a method of treating a viral infection in a human, comprising administering to the human a composition comprising cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, wherein an effect on the viral infection of an amount of tenofovir alafenamide hemifumarate in the composition is greater than the effect of the same amount of tenofovir alafenamide hemifumarate in the absence of cobicistat, or a pharmaceutically acceptable salt thereof, and wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0129] In one embodiment, the invention provides an anti-viral treatment method on a viral infection in a human, comprising administering to the human a composition comprising cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, wherein the composition contains an amount of cobicistat, or a pharmaceutically acceptable salt thereof, sufficient for an amount of tenofovir alafenamide hemifumarate in the composition to provide an anti-viral effect that is greater than the anti-viral effect of the amount of tenofovir alafenamide hemifumarate in the absence of cobicistat, or a pharmaceutically acceptable salt thereof, and wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0130] In one embodiment, the invention provides an anti-viral treatment method on a viral infection in a human, comprising administering to the human a composition comprising cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, wherein an anti-viral effect of an amount of tenofovir alafenamide hemifumarate in the composition is greater than the anti-viral effect of the same amount of tenofovir alafenamide hemifumarate in the absence of cobicistat, or a pharmaceutically acceptable salt thereof, and wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0131] In one embodiment, the invention provides a composition comprising: cobicistat, or a pharmaceutically acceptable salt thereof; and tenofovir alafenamide hemifumarate. In a further embodiment, the composition comprises: 50-500 mg of cobicistat, or a pharmaceutically acceptable salt thereof; and 3-40 mg of tenofovir alafenamide hemifumarate. In another embodiment, the composition further comprises a pharmaceutically acceptable carrier or diluent.

[0132] In one embodiment, the invention provides a method of treating a viral infection in a human comprising administering a composition comprising: cobicistat, or a pharmaceutically acceptable salt thereof; and tenofovir alafenamide hemifumarate, to the human.

[0133] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, to the human.

[0134] In one embodiment, the invention provides a method of inhibiting activity of a retroviral reverse transcriptase comprising coadministering cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate. In a further embodiment, the coadministering of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, is in a human.

[0135] In one embodiment, the invention provides use of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, for the prophylactic or therapeutic treatment of a viral infection in a human.

[0136] In one embodiment, the invention provides use of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, for the manufacture of a medicament for treating a viral infection in a human.

[0137] In one embodiment, the invention provides use of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase. In a further embodiment, the medicament is for inhibiting activity of a retroviral reverse transcriptase in a human.

[0138] In one embodiment, the invention provides a method of boosting an anti-viral effect of tenofovir alafenamide hemifumarate in a human comprising administering a composition comprising: cobicistat, or a pharmaceutically acceptable salt thereof; and tenofovir alafenamide hemifumarate, to the human.

[0139] In one embodiment, the invention provides a method of boosting an anti-viral effect of tenofovir alafenamide hemifumarate in a human comprising coadministering cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate to the human. In a further embodiment, 50-500 mg of cobicistat, or a pharmaceutically acceptable salt thereof, is coadministered with 3-40 mg of tenofovir alafenamide hemifumarate.

[0140] In one embodiment, the invention provides a method of inhibiting Pgp-mediated intestinal secretion of tenofovir alafenamide hemifumarate in a human comprising administering a composition comprising: cobicistat, or a pharmaceutically acceptable salt thereof; and tenofovir alafenamide hemifumarate, to the human.

[0141] In one embodiment, the invention provides a method of inhibiting Pgp-mediated intestinal secretion of tenofovir alafenamide hemifumarate in a human by coadministration of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate. In a further embodiment, 50-500 mg of cobicistat, or a pharmaceutically acceptable salt thereof, is coadministered with 3-40 mg of tenofovir alafenamide hemifumarate.

[0142] In additional embodiments, the invention provides the methods and uses disclosed wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0143] In one embodiment, the invention provides a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir. In a further embodiment, the composition comprises: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir. In a further embodiment, the invention provides a method of treating a viral infection in a human comprising administering such a composition to the human.

[0144] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir to the human. In a further embodiment, the method comprises coadministering (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir to the human.

[0145] In one embodiment, the invention provides use of a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir, for the prophylactic or therapeutic treatment of a viral infection in a human.

[0146] In one embodiment, the invention provides use of (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir for the manufacture of a medicament for treating a viral infection in a human. In a further embodiment, the invention

provides use of (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir for the manufacture of a medicament for treating a viral infection in a human.

[0147] In one embodiment, the invention provides a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0148] In one embodiment, the invention provides a composition comprising: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0149] In additional embodiments, the invention provides the methods and uses disclosed wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0150] In one embodiment, the invention provides a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) darunavir. In a further embodiment, the composition comprises: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 400-1600 mg darunavir. In a further embodiment, the invention provides a method of treating a viral infection in a human comprising administering such a composition to the human.

[0151] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) darunavir to the human. In a further embodiment, the method comprises coadministering (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 400-1600 mg darunavir to the human.

[0152] In one embodiment, the invention provides use of a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) darunavir, for the prophylactic or therapeutic treatment of a viral infection in a human.

[0153] In one embodiment, the invention provides use of (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) darunavir for the manufacture of a medicament for treating a viral infection in a human. In a further embodiment, the invention provides use of (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 400-1600 mg darunavir for the manufacture of a medicament for treating a viral infection in a human.

[0154] In one embodiment, the invention provides a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) darunavir for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0155] In one embodiment, the invention provides a composition comprising: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 400-1600 mg darunavir for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0156] In additional embodiments, the invention provides the methods and uses disclosed wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0157] In one embodiment, the invention provides a composition comprising: tenofovir alafenamide hemifumarate and emtricitabine. In a further embodiment, the composition comprises: 3-40 mg tenofovir alafenamide hemifumarate and 50-500 mg emtricitabine. In a further embodiment, the invention provides a method of treating a viral infection in a human comprising administering such a composition to the human.

[0158] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering tenofovir alafenamide hemifumarate and emtricitabine to the human. In a further embodiment, the method comprises coadministering 3-40 mg tenofovir alafenamide hemifumarate and 50-500 mg emtricitabine to the human.

[0159] In one embodiment, the invention provides use of a composition comprising: tenofovir alafenamide hemifumarate and emtricitabine for the prophylactic or therapeutic treatment of a viral infection in a human.

[0160] In one embodiment, the invention provides use of tenofovir alafenamide hemifumarate and emtricitabine for the manufacture of a medicament for treating a viral infection in a human. In a further embodiment, the invention provides use of 3-40 mg tenofovir alafenamide hemifumarate and 50-500 mg emtricitabine for the manufacture of a medicament for treating a viral infection in a human.

[0161] In one embodiment, the invention provides a composition comprising: tenofovir alafenamide hemifumarate and emtricitabine for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0162] In one embodiment, the invention provides a composition comprising: 3-40 mg tenofovir alafenamide hemifumarate and 50-500 mg emtricitabine for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0163] In additional embodiments, the invention provides the methods and uses disclosed wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0164] In one embodiment, the invention provides a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) rilpivirine; and (c) emtricitabine. In a further embodiment, the composition comprises: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 10-80 mg rilpivirine; and (c) 50-500 mg emtricitabine. In a further embodiment, the invention provides a method of treating a viral infection in a human comprising administering such a composition to the human.

[0165] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering (a) tenofovir alafenamide hemifumarate; (b) rilpivirine; and (c) emtricitabine to the human. In a further embodiment, the method comprises coadministering (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 10-80 mg rilpivirine; and (c) 50-500 mg emtricitabine to the human.

[0166] In one embodiment, the invention provides use of a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) rilpivirine; and (c) emtricitabine, for the prophylactic or therapeutic treatment of a viral infection in a human.

[0167] In one embodiment, the invention provides use of (a) tenofovir alafenamide hemifumarate; (b) rilpivirine; and (c) emtricitabine for the manufacture of a medicament for treating a viral infection in a human. In a further embodiment, the invention provides use of (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 10-80 mg rilpivirine; and (c) 50-500 mg emtricitabine for the manufacture of a medicament for treating a viral infection in a human.

[0168] In one embodiment, the invention provides a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) rilpivirine; and (c) emtricitabine for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0169] In one embodiment, the invention provides a composition comprising: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 10-80 mg rilpivirine; and (c) 50-500 mg emtricitabine for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0170] In additional embodiments, the invention provides the methods and uses disclosed wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0171] In one embodiment, the invention provides a composition comprising: tenofovir alafenamide hemifumarate and GS-9441. In a further embodiment, the composition comprises: 3-40 mg tenofovir alafenamide hemifumarate and 5-1500 mg GS-9441. In a further embodiment, the invention provides a method of

treating a viral infection in a human comprising administering such a composition to the human.

[0172] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering tenofovir alafenamide hemifumarate and GS-9441 to the human. In a further embodiment, the method comprises coadministering 3-40 mg tenofovir alafenamide hemifumarate and 5-1500 mg GS-9441 to the human.

[0173] In one embodiment, the invention provides use of a composition comprising: tenofovir alafenamide hemifumarate and GS-9441 for the prophylactic or therapeutic treatment of a viral infection in a human.

[0174] In one embodiment, the invention provides use of tenofovir alafenamide hemifumarate and GS-9441 for the manufacture of a medicament for treating a viral infection in a human. In a further embodiment, the invention provides use of 3-40 mg tenofovir alafenamide hemifumarate and 5-1500 mg GS-9441 for the manufacture of a medicament for treating a viral infection in a human.

[0175] In one embodiment, the invention provides a composition comprising: tenofovir alafenamide hemifumarate and GS-9441 for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0176] In one embodiment, the invention provides a composition comprising: 3-40 mg tenofovir alafenamide hemifumarate and 5-1500 mg GS-9441 for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0177] In additional embodiments, the invention provides the methods and uses disclosed wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

BRIEF DESCRIPTION OF THE DRAWINGS

[0178] Figure 1 shows pharmacokinetic data from patients dosed with various doses of GS-7340 and TDF.

[0179] Figure 2 shows pharmacokinetic data from patients dosed with various doses of GS-7340 and TDF.

[0180] Figure 3A-B shows pharmacokinetic data from patients dosed with various formulations of GS-7340.

[0181] Figure 4A-B shows pharmacokinetic data from patients dosed with various formulations of GS-7340.

[0182] Figure 5A-B shows pharmacokinetic data from patients dosed with various formulations of GS-7340.

[0183] Figure 6 shows pharmacokinetic data from patients dosed with various formulations of GS-7340.

[0184] Figure 7 shows pharmacokinetic data from patients dosed with various formulations of GS-7340.

[0185] Figure 8 shows pharmacokinetic data from patients dosed with various formulations of GS-7340.

[0186] Figure 9 shows pharmacokinetic data from patients dosed with various formulations of GS-7340.

[0187] Figure 10A-B shows results of substrate assays in cells transfected with the genes for human P-glycoprotein (Pgp; MDR1) and breast cancer resistance protein (BCRP) genes.

[0188] Figure 11A-B shows results of bidirectional permeability assays in cells transfected with the genes for human Pgp and BCRP.

[0189] Figure 12A-F shows results of bidirectional permeability assays in cells transfected with the genes for human Pgp and BCRP.

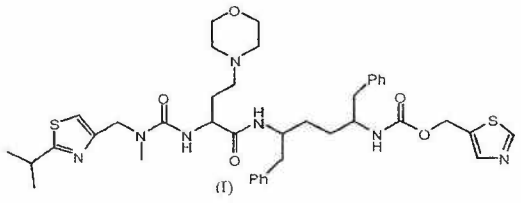
[0190] Figure 13 shows the X-ray powder diffraction (XRPD) pattern of tenofovir alafenamide hemifumarate.

[0191] Figure 14 shows a graph of the DSC analysis of tenofovir alafenamide hemifumarate.

[0192] Figure 15 shows a graph of the thermogravimetric analysis (TGA) data for tenofovir alafenamide hemifumarate.

[0193] Figure 16 shows a graph of the dynamic vapor sorption (DVS) analysis of tenofovir alafenamide hemifumarate.

DETAILED DESCRIPTION OF THE INVENTION

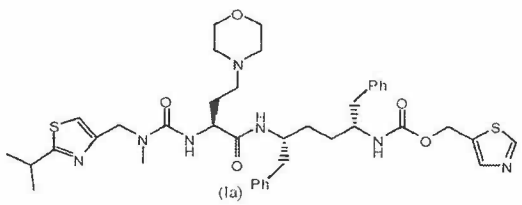


(I)

[0194] Cobicistat (chemical name 1,3-thiazol-5-ylmethyl (2R,5R)-(5-{[(2S)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]]-4-(morpholin-4-yl)butanamido}-1,6-diphenylhexan-2-yl)carbamate) is a chemical entity that has been shown to be a mechanism-based inhibitor that irreversibly inhibits CYP3A enzymes.

[0195] Detailed enzyme inactivation kinetic studies were performed comparing cobicistat with ritonavir. Cobicistat was found to be an efficient inactivator of human hepatic microsomal CYP3A activity with kinetic parameters similar to those of ritonavir. In addition, cobicistat is a moderate inhibitor of CYP2B6 (similar potency to ritonavir), a weak inhibitor of CYP2D6, and does not appreciably inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, or uridine glucuronosyltransferase 1A1. In xenobiotic receptor transactivation and human hepatocyte studies, cobicistat displayed no/weak potential as an inducer of cytochrome P450, UGT1A1, or P-glycoprotein (at up to 30 μM). Permeability assays suggest that cobicistat is not a strong substrate or inhibitor of transporters including P-glycoprotein, MRP1, and MRP2. Inhibition of intestinal P-glycoprotein by cobicistat is only possible during absorption due to its high aqueous solubility, but it is not potent enough to inhibit transporters at systemic concentrations. These data indicate that, compared to ritonavir, cobicistat is a more selective inhibitor of CYP3A *in vitro* and a weaker inducer of CYP enzymes, which may potentially result in fewer clinically significant interactions with substrates of other CYP enzymes.

[0196] Cobicistat may also be present in compositions enriched with a stereoisomer of formula (Ia):



(Ia)

which is thiazol-5-ylmethyl (2R,5R)-5-((S)-2-(3-((2-isopropylthiazol-5-yl)methyl)-3-methylureido)-4-morpholinobutanamido)-1,6-diphenylhexan-2-ylcarbamate.

[0197] In one embodiment, the cobicistat has an enriched concentration of 85 ± 5% of the stereoisomer of formula (Ia). In another embodiment, the cobicistat has an enriched concentration of 90 ± 5% of the stereoisomer of formula (Ia). In another embodiment, the cobicistat has an enriched concentration of 95 ± 2% of the stereoisomer of formula (Ia). In another embodiment, the cobicistat has an enriched concentration of 99 ± 1% of the stereoisomer of formula (Ia). In another embodiment, the cobicistat is present as the pure stereoisomer of formula (Ia).

[0198] Coadministration of cobicistat with GS-7340 or tenofovir alafenamide hemifumarate boosts systemic exposure to GS-7340 or tenofovir alafenamide hemifumarate in humans, improves the pharmacokinetics of GS-7340 or tenofovir alafenamide hemifumarate (including, but not limited to, C_{max} increases), and increases blood levels of GS-7340 / tenofovir alafenamide hemifumarate / tenofovir. Therefore, GS-7340 or tenofovir alafenamide hemifumarate coadministered with cobicistat may be administered in lower amounts than previously thought to achieve a therapeutic effect. Such lower amounts may be amounts that would be subtherapeutic in the absence of coadministration of cobicistat.

[0199] Without being bound by any theory of the invention, it is believed that cobicistat may be acting to inhibit intestinal Pgp-mediated intestinal secretion of GS-7340 or tenofovir alafenamide hemifumarate. In *in vitro* studies, cobicistat and ritonavir significantly increased the accumulation of probe substrates (such as

calcein AM and Hoechst 33342) in cells transfected with P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP), and cobicistat was found to be a substrate for these transporters. Cobicistat appears to be a substrate of Pgp and BCRP and likely has a competitive mode of inhibition with coadministered agents. Cobicistat appears to be a relatively weak inhibitor of Pgp and BCRP and may only have a transient effect on these transporters during intestinal absorption, facilitated by high solubility of, and resulting high concentrations of, cobicistat achievable in the gastrointestinal tract. Combined, these results suggest that cobicistat can effectively inhibit intestinal transporters and increase the absorption of coadministered substrates, including HIV protease inhibitors and GS-7340 or tenofovir alafenamide hemifumarate, contributing to its effectiveness as a pharmacoenhancer.

[0200] As used herein, the term "coadminister" (or "coadministration") refers to administration of two or more agents within a 24-hour period of each other, for example, as part of a clinical treatment regimen. In other embodiments, "coadminister" refers to administration of two or more agents within 2 hours of each other. In other embodiments, "coadminister" refers to administration of two or more agents within 30 minutes of each other. In other embodiments, "coadminister" refers to administration of two or more agents within 15 minutes of each other. In other embodiments, "coadminister" refers to administration of two or more agents at the same time, either as part of a single formulation or as multiple formulations that are administered by the same or different routes.

[0201] The term "unit dosage form" refers to a physically discrete unit, such as a capsule, tablet, or solution, that is suitable as a unitary dosage for a human patient, each unit containing a predetermined quantity of one or more active ingredient(s) calculated to produce a therapeutic effect, in association with at least one pharmaceutically acceptable diluent or carrier, or combination thereof. Unit dosage formulations contain a daily dose or unit daily subdose or an appropriate fraction thereof, of the active ingredient(s).

[0202] The term "subtherapeutic amount" of a compound is any amount of the compound that upon dosing is insufficient to achieve the desired therapeutic benefit.

[0203] The term "boosting amount" or "boosting dose" is the amount of a compound needed to improve the pharmacokinetics of a second compound (or increase availability or exposure). The boosting amount or boosting dose may improve the pharmacokinetics (or increase availability or exposure) of the second compound to a level that is therapeutic in a subject. In other words, a subtherapeutic amount of the second compound (i.e., subtherapeutic when administered without coadministration of the boosting amount) reaches a therapeutic level(s) in a subject due to improved pharmacokinetics (or increased availability or exposure) upon coadministration of the boosting amount.

[0204] The present invention also provides a method for the treatment or prophylaxis of diseases, disorders, and conditions. An example of a disease, disorder, or condition includes, but is not limited to, a retrovirus infection, or a disease, disorder, or condition associated with a retrovirus infection. Retroviruses are RNA viruses and are generally classified into the alpharetrovirus, betaretrovirus, deltaretrovirus, epsilonretrovirus, gammaretrovirus, lentivirus, and spumavirus families. Examples of retroviruses include, but are not limited to, human immunodeficiency virus (HIV), human T-lymphotropic virus (HTLV), rous sarcoma virus (RSV), and the avian leukosis virus. In general, three genes of the retrovirus genome code for the proteins of the mature virus: *gag* (group-specific antigen) gene, which codes for the core and structural proteins of the virus; *pol* (polymerase) gene, which codes for the enzymes of the virus, including reverse transcriptase, protease, and integrase; and *env* (envelope) gene, which codes for the retrovirus surface proteins.

[0205] Retroviruses attach to and invade a host cell by releasing a complex of RNA and the *pol* products, among other things, into the host cell. The reverse transcriptase then produces double-stranded DNA from the viral RNA. The double-stranded DNA is imported into the nucleus of the host cell and integrated into the host cell genome by the viral integrase. A nascent virus from the integrated DNA is formed when the integrated viral DNA is converted into mRNA by the host cell polymerase, and the proteins necessary for virus formation are produced by the action of the virus protease. The virus particle undergoes budding and is released from the host cell to form a mature virus.

[0206] The active agents may be administered to a human in any conventional manner. While it is possible for the active agents to be administered as raw compounds, they are preferably administered as a pharmaceutical composition. The salt, carrier, or diluent should be acceptable in the sense of being compatible with the other ingredients and not deleterious to the recipient thereof. Examples of carriers or diluents for oral administration include cornstarch, lactose, magnesium stearate, talc, microcrystalline cellulose, stearic acid, povidone, crospovidone, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose (e.g., low substituted hydroxypropyl cellulose), hydroxypropylmethyl cellulose (e.g., hydroxypropylmethyl cellulose 2910), and sodium lauryl sulfate.

[0207] The pharmaceutical compositions may be prepared by any suitable method, such as those methods well known in the art of pharmacy, for example, methods such as those described in Gennaro et al., Remington's Pharmaceutical Sciences (18th ed., Mack Publishing Co., 1990), especially Part 8: Pharmaceutical Preparations and their Manufacture. Such methods include the step of bringing into association GS-7340 or tenofovir alafenamide hemifumarate with the carrier or diluent and optionally one or more accessory ingredients. Such accessory ingredients include those conventional in the art, such as, fillers, binders, excipients, disintegrants, lubricants, colorants, flavoring agents, sweeteners, preservatives (e.g., antimicrobial preservatives). suspending agents, thickening agents, emulsifying agents, and/or wetting agents.

[0208] The term "GS-7340, or pharmaceutically acceptable salt thereof" or the like includes any amorphous, crystalline, co-crystalline, complex, or other physical form thereof. In one embodiment, a composition comprising a pharmaceutically acceptable coformer and GS-7340 is administered. The pharmaceutically acceptable coformer can be any pharmaceutically acceptable compound that is capable of forming a "pharmaceutically acceptable salt" with GS-7340. For example, the pharmaceutically acceptable coformer can be a pharmaceutically acceptable acid (e.g. adipic acid, L-aspartic acid, citric acid, fumaric acid, maleic acid, malic acid, malonic acid, succinic acid, tartaric acid, or oxalic acid). In one embodiment of the invention, the pharmaceutically acceptable coformer is a bis-acid. In another embodiment, the pharmaceutically acceptable coformer is

fumaric acid. In another embodiment, a composition comprising a coformer and GS-7340 in a ratio of about 0.5 ± 0.05 can be administered. One form of GS-7340 is a hemifumarate form (tenofovir alafenamide hemifumarate), as described further herein.

[0209] The pharmaceutical compositions may provide controlled, slow release or sustained release of the agents (e.g., GS-7340 or tenofovir alafenamide hemifumarate) over a period of time. The controlled, slow release or sustained release of the agents (e.g., GS-7340 or tenofovir alafenamide hemifumarate) may maintain the agents in the bloodstream of the human for a longer period of time than with conventional formulations. Pharmaceutical compositions include, but are not limited to, coated tablets, pellets, solutions, powders, capsules, and dispersions of GS-7340 or tenofovir alafenamide hemifumarate in a medium that is insoluble in physiologic fluids, or where the release of the therapeutic compound follows degradation of the pharmaceutical composition due to mechanical, chemical, or enzymatic activity.

[0210] The pharmaceutical compositions of the invention may be, for example, in the form of a pill, capsule, solution, powder, or tablet, each containing a predetermined amount of GS-7340 or tenofovir alafenamide hemifumarate. In an embodiment of the invention, the pharmaceutical composition is in the form of a tablet comprising GS-7340 or tenofovir alafenamide hemifumarate. In another embodiment of the invention, the pharmaceutical composition is in the form of a tablet comprising GS-7340 and the components of the tablet utilized and described in the Examples provided herein.

[0211] For oral administration, fine powders or granules may contain diluting, dispersing, and or surface active agents and may be present, for example, in water or in a syrup, in capsules or sachets in the dry state, or in a nonaqueous solution or suspension wherein suspending agents may be included, or in tablets wherein binders and lubricants may be included.

[0212] When administered in the form of a liquid solution or suspension, the formulation may contain GS-7340 or tenofovir alafenamide hemifumarate and purified water. Optional components in the liquid solution or suspension include suitable sweeteners, flavoring agents, preservatives (e.g., antimicrobial

preservatives), buffering agents, solvents, and mixtures thereof. A component of the formulation may serve more than one function. For example, a suitable buffering agent also may act as a flavoring agent as well as a sweetener.

[0213] Suitable sweeteners include, for example, saccharin sodium, sucrose, and mannitol. A mixture of two or more sweeteners may be used. The sweetener or mixtures thereof are typically present in an amount of from about 0.001% to about 70% by weight of the total composition. Suitable flavoring agents may be present in the pharmaceutical composition to provide a cherry flavor, cotton candy flavor, or other suitable flavor to make the pharmaceutical composition easier for a human to ingest. The flavoring agent or mixtures thereof are typically present in an amount of about 0.0001% to about 5% by weight of the total composition.

[0214] Suitable preservatives include, for example, methylparaben, propylparaben, sodium benzoate, and benzalkonium chloride. A mixture of two or more preservatives may be used. The preservative or mixtures thereof are typically present in an amount of about 0.0001% to about 2% by weight of the total composition.

[0215] Suitable buffering agents include, for example, citric acid, sodium citrate, phosphoric acid, potassium phosphate, and various other acids and salts. A mixture of two or more buffering agents may be used. The buffering agent or mixtures thereof are typically present in an amount of about 0.001% to about 4% by weight of the total composition.

[0216] Suitable solvents for a liquid solution or suspension include, for example, sorbitol, glycerin, propylene glycol, and water. A mixture of two or more solvents may be used. The solvent or solvent system is typically present in an amount of about 1% to about 90% by weight of the total composition.

[0217] The pharmaceutical composition may be coadministered with adjuvants. For example, nonionic surfactants such as polyoxyethylene oleyl ether and n-hexadecyl polyethylene ether may be administered with or incorporated into the pharmaceutical composition to artificially increase the permeability of the intestinal walls. Enzymatic inhibitors may also be administered with or incorporated into the pharmaceutical composition.

GS-7340

[0218] In one embodiment of the invention, a dose of 3 mg, 3 ± 2 mg, or 3 ± 1 mg of GS-7340, or a pharmaceutically acceptable salt thereof, is administered.

[0219] In one embodiment of the invention, a dose of 8 ± 3 mg, 8 ± 2 mg or 8 ± 1 mg of GS-7340, or a pharmaceutically acceptable salt thereof, is administered.

[0220] In one embodiment of the invention, a unit dosage form comprises a dose of 8 ± 2 mg of GS-7340, or a pharmaceutically acceptable salt thereof.

[0221] In various embodiments of the invention, a dose of 8 ± 3 mg; 25 ± 10 mg; 10 ± 5 mg; 25 ± 5 mg; 25 ± 2 mg; 40 ± 10 mg; 40 ± 5 mg; 40 ± 2 mg; 60 ± 20 mg; 60 ± 10 mg; 100 ± 20 mg; 100 ± 10 mg; 125 ± 20 mg; 125 ± 10 mg; 150 ± 20 mg; 150 ± 10 mg; 200 ± 40 mg; or 200 ± 15 mg of GS-7340, or a pharmaceutically acceptable salt thereof, is administered.

[0222] The desired daily dose of GS-7340 also may be administered as two, three, four, five, six, or more subdoses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

[0223] The concentration of tenofovir / GS-7340 in the bloodstream may be measured as the plasma concentration (e.g., ng/mL). Pharmacokinetic parameters for determining the plasma concentration include, but are not limited to, the maximum observed plasma concentration (C_{max}), observed plasma concentration at the end of the dosing interval or "trough" concentration (C_{tau} or C_{min}), area under the plasma concentration time curve (AUC) from time zero up to the last quantifiable time point ($AUC_{0\text{-}last}$), AUC from time zero to infinity ($AUC_{0\text{-}inf}$), AUC over the dosing interval (AUC_{tau}), time of maximum observed plasma concentration after administration (t_{max}), and half-life of GS-7340 in plasma ($t_{1/2}$).

[0224] Administration of GS-7340 with food according to the methods of the invention may also increase absorption of GS-7340. Absorption of GS-7340 may be measured by the concentration attained in the bloodstream over time after administration of GS-7340. An increase in absorption by administration of GS-7340 with food may also be evidenced by an increase in C_{max} and/or AUC of GS-7340 as compared to the values if GS-7340 was administered without food. Typically protease inhibitors are administered with food.

Tenofovir alafenamide hemifumarate

[0225] In one embodiment, there is provided a hemifumarate form of tenofovir alafenamide (i.e., tenofovir alafenamide hemifumarate). This form may have a ratio (i.e., a stoichiometric ratio or mole ratio) of fumaric acid to tenofovir alafenamide of 0.5 ± 0.1, 0.5 ± 0.05, 0.5 ± 0.01, or about 0.5, or the like.

[0226] In one embodiment, tenofovir alafenamide hemifumarate consists of fumaric acid and tenofovir alafenamide in a ratio of 0.5 ± 0.1.

[0227] In one embodiment, tenofovir alafenamide hemifumarate consists essentially of fumaric acid and tenofovir alafenamide in a ratio of 0.5 ± 0.1.

[0228] In one embodiment, tenofovir alafenamide hemifumarate has an XRPD pattern comprising 2theta values of 6.9 ± 0.2°, 8.6 ± 0.2°, 10.0 ± 0.2°, 11.0 ± 0.2°, 12.2 ± 0.2°, 15.9 ± 0.2°, 16.3 ± 0.2°, 20.2 ± 0.2°, and 20.8 ± 0.2°.

[0229] In one embodiment, tenofovir alafenamide hemifumarate has an XRPD pattern comprising at least four 2theta values selected from 6.9 ± 0.2°, 8.6 ± 0.2°, 10.0 ± 0.2°, 11.0 ± 0.2°, 12.2 ± 0.2°, 15.9 ± 0.2°, 16.3 ± 0.2°, 20.2 ± 0.2°, and 20.8 ± 0.2°.

[0230] In one embodiment, tenofovir alafenamide hemifumarate has a DSC onset endotherm of 131 ± 2 °C, or 131 ± 1 °C.

[0231] In various embodiments, a tenofovir alafenamide hemifumarate composition comprises less than about 5%; 1%; or 0.5% by weight of tenofovir alafenamide monofumarate.

[0232] In one embodiment, a tenofovir alafenamide hemifumarate composition comprises no detectable tenofovir alafenamide monofumarate.

[0233] Tenofovir alafenamide (i.e., the compound 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine) can be prepared as described in U.S. Patent No. 7,390,791.

[0234] In various embodiments of the invention, a dose of 3 mg; 3 ± 2 mg; 3 ± 1 mg; 8 ± 3 mg; 8 ± 2 mg; 8 ± 1 mg;

[0235] In one embodiment of the invention, a unit dosage form comprises a dose of 8 ± 2 mg of tenofovir alafenamide hemifumarate.

[0236] 25 ± 10 mg; 10 ± 5 mg; 10 mg; 25 ± 5 mg; 25 ± 2 mg; 40 ± 10 mg; 40 ± 5 mg; 40 ± 2 mg; 60 ± 20 mg; 60 ± 10 mg; 100 ± 20 mg; 100 ± 10 mg;

125 ± 20 mg; 125 ± 10 mg; 150 ± 20 mg; 150 ± 10 mg; 200 ± 40 mg; or 200 ± 15 mg of tenofovir alafenamide hemifumarate is administered.

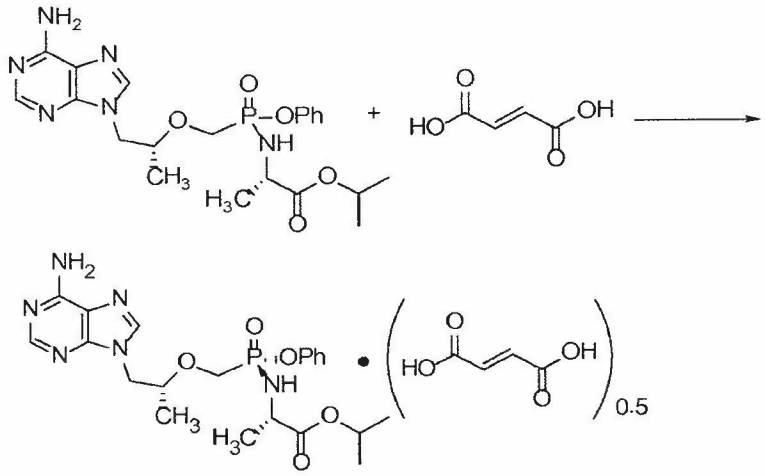
[0237] The desired daily dose of tenofovir alafenamide hemifumarate also may be administered as two, three, four, five, six, or more subdoses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

[0238] The concentration of tenofovir, GS-7340, or tenofovir alafenamide hemifumarate in the bloodstream may be measured as the plasma concentration (e.g., ng/mL). Pharmacokinetic parameters for determining the plasma concentration include, but are not limited to, the maximum observed plasma concentration (C_{max}), observed plasma concentration at the end of the dosing interval or "trough" concentration (C_{tau} or C_{min}), area under the plasma concentration time curve (AUC) from time zero up to the last quantifiable time point ($AUC_{0\text{-}last}$), AUC from time zero to infinity ($AUC_{0\text{-}inf}$), AUC over the dosing interval (AUC_{tau}), time of maximum observed plasma concentration after administration (t_{max}), and half-life of tenofovir, GS-7340, or tenofovir alafenamide hemifumarate in plasma ($t_{1/2}$).

[0239] Administration of GS-7340 or tenofovir alafenamide hemifumarate with food according to the methods of the invention may also increase absorption of GS-7340 or tenofovir alafenamide hemifumarate. Absorption of GS-7340 or tenofovir alafenamide hemifumarate may be measured by the concentration attained in the bloodstream over time after administration of GS-7340 or tenofovir alafenamide hemifumarate. An increase in absorption by administration of GS-7340 or tenofovir alafenamide hemifumarate with food may also be evidenced by an increase in C_{max} and/or AUC of GS-7340 or tenofovir alafenamide hemifumarate as compared to the values if GS-7340 or tenofovir alafenamide hemifumarate was administered without food. Typically protease inhibitors are administered with food.

Selective Crystallization – Tenofovir alafenamide hemifumarate

[0240] In one embodiment, tenofovir alafenamide hemifumarate can be prepared using selective crystallization. An example of a scheme for this preparation method is as follows.



[0241] The method can be carried out by subjecting a solution comprising: a) a suitable solvent; b) fumaric acid; c) tenofovir alafenamide; and, optionally, d) one or more seeds comprising tenofovir alafenamide hemifumarate, to conditions that provide for the crystallization of fumaric acid and tenofovir alafenamide. The starting solution can contain the single diastereomer of tenofovir alafenamide or a mixture of tenofovir alafenamide and one or more of its other diastereomers (e.g., GS-7339, as described in U.S. Patent No. 7,390,791).

[0242] The selective crystallization can be carried out in any suitable solvent. For example, it can be carried out in a protic solvent or in an aprotic organic solvent, or in a mixture thereof. In one embodiment, the solvent comprises a protic solvent (e.g., water or isopropyl alcohol). In another embodiment, the solvent comprises an aprotic organic solvent (e.g., acetone, acetonitrile (ACN), toluene, ethyl acetate, isopropyl acetate, heptane, tetrahydrofuran (THF), 2-methyl THF, methyl ethyl ketone, or methyl isobutyl ketone, or a mixture thereof). In one embodiment, the

solvent comprises ACN or a mixture of ACN and up to about 50% methylene chloride (by volume). The selective crystallization also can be carried out at any suitable temperature, for example, a temperature in the range of from about 0 °C to about 70 °C. In one specific embodiment, the resolution is carried out at a temperature of about 0 °C.

[0243] One major advantage of the hemifumarate form of tenofovir alafenamide over the monofumarate form is its exceptional capability to purge GS-7339 (i.e., 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine; described in, e.g., U.S. Patent No. 7,390,791), which is the major diastereomeric impurity in the active pharmaceutical ingredient. Thus, the hemifumarate form of tenofovir alafenamide can be more readily and easily separated from impurities than the monofumarate form. Other major advantages of tenofovir alafenamide hemifumarate over the monofumarate form include improved thermodynamic and chemical stability (including long-term storage stability), superior process reproducibility, superior drug product content uniformity, and a higher melting point.

[0244] Tenofovir alafenamide hemifumarate is useful in the treatment and/or prophylaxis of one or more viral infections in man or animals, including infections caused by DNA viruses. RNA viruses, herpesviruses (e.g., CMV, HSV 1, HSV 2, VZV), retroviruses, hepadnaviruses (e.g., HBV), papillomavirus, hantavirus, adenoviruses and HIV. U.S. Patent No. 6,043,230 (incorporated by reference herein in its entirety) and other publications describe the anti-viral specificity of nucleotide analogs, such as tenofovir disoproxil. Like tenofovir disoproxil, tenofovir alafenamide is another prodrug form of tenofovir, and can be used in the treatment and/or prophylaxis of the same conditions.

[0245] Tenofovir alafenamide hemifumarate can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including ocular, buccal, and sublingual), vaginal, and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal, and epidural). Generally, tenofovir alafenamide hemifumarate is administered orally, but it can be administered by any of the other routes noted herein.

[0246] Accordingly, pharmaceutical compositions include those suitable for topical or systemic administration, including oral, rectal, nasal, buccal, sublingual, vaginal, or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal, and epidural) administration. The formulations are in unit dosage form and are prepared by any of the methods well known in the art of pharmacy.

[0247] For oral therapeutic administration, the tenofovir alafenamide hemifumarate may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such pharmaceutical compositions and preparations will typically contain at least 0.1% of tenofovir alafenamide hemifumarate. The percentage of this active compound in the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% or more of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful pharmaceutical compositions is preferably such that an effective dosage level will be obtained upon administration of a single-unit dosage (e.g., tablet). Other dosage formulations may provide therapeutically effective amounts of tenofovir alafenamide hemifumarate upon repeated administration of subclinically effective amounts of the same. Preferred unit dosage formulations include those containing a daily dose (e.g., a single daily dose), as well as those containing a unit daily subclinical dose, or an appropriate fraction thereof (e.g., multiple daily doses), of tenofovir alafenamide hemifumarate.

[0248] Pharmaceutical compositions suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, each containing a predetermined amount of tenofovir alafenamide hemifumarate; as a powder or granules; as a solution or a suspension in an aqueous liquid or a nonaqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. Tenofovir alafenamide hemifumarate may also be presented as a bolus, electuary, or paste.

[0249] Tenofovir alafenamide hemifumarate is preferably administered as part of a pharmaceutical composition or formulation. Such pharmaceutical composition or formulation comprises tenofovir alafenamide hemifumarate together with one or

more pharmaceutically acceptable carriers / excipients, and optionally other therapeutic ingredients. The excipient(s) / carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the patient. Excipients include, but are not limited to, substances that can serve as a vehicle or medium for tenofovir alafenamide hemifumarate (e.g., a diluent carrier). They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet.

[0250] Accordingly, the tablets, troches, pills, capsules, and the like may also contain, without limitation, the following: a binder(s), such as hydroxypropyl cellulose, povidone, or hydroxypropyl methylcellulose; a filler(s), such as microcrystalline cellulose, pregelatinized starch, starch, mannitol, or lactose monohydrate; a disintegrating agent(s), such as croscarmellose sodium, cross-linked povidone, or sodium starch glycolate; a lubricant(s), such as magnesium stearate, stearic acid, or other metallic stearates; a sweetening agent(s), such as sucrose, fructose, lactose, or aspartame; and/or a flavoring agent(s), such as peppermint, oil of wintergreen, or a cherry flavoring. When the unit dosage form is a capsule, it may contain, in addition to materials of the above types, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, polymers, wax, shellac, or sugar and the like. Of course, any material used in preparing any unit dosage form typically will be pharmaceutically acceptable and substantially nontoxic in the amounts employed. In addition, tenofovir alafenamide hemifumarate may be incorporated into sustained-release preparations and devices.

[0251] For infections of the eye or other external tissues, e.g., mouth and skin, the pharmaceutical compositions are preferably applied as a topical ointment or cream containing tenofovir alafenamide hemifumarate in an amount of, for example, 0.01 to 10% w/w (including active ingredient in a range between 0.1% and 5% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 3% w/w and most preferably 0.5 to 2% w/w. When formulated in an ointment,

the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base.

[0252] Pharmaceutical compositions suitable for topical administration in the mouth include lozenges comprising tenofovir alafenamide hemifumarate in a flavored basis, for example, sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0253] Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

[0254] Pharmaceutical formulations suitable for parenteral administration are sterile and include aqueous and nonaqueous injection solutions that may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and nonaqueous sterile suspensions that may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials with elastomeric stoppers, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier (e.g., water for injections) immediately prior to use. Injection solutions and suspensions may be prepared from sterile powders, granules, and tablets of the kind previously described.

[0255] In addition to the ingredients particularly mentioned above, the pharmaceutical compositions / formulations may include other ingredients conventional in the art, having regard to the type of formulation in question.

[0256] In another embodiment, there is provided veterinary compositions comprising tenofovir alafenamide hemifumarate together with a veterinary carrier therefor. Veterinary carriers are materials useful for the purpose of administering the composition to cats, dogs, horses, rabbits, and other animals, and may be solid, liquid, or gaseous materials that are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally, or by any other desired route.

[0257] The tenofovir alafenamide hemifumarate can be used to provide controlled release pharmaceutical formulations containing a matrix or absorbent material and an active ingredient of the invention, in which the release of the active ingredient can be controlled and regulated to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the compound. Controlled release formulations adapted for oral administration, in which discrete units comprising a compounds of the invention, can be prepared according to conventional methods.

[0258] Useful dosages of tenofovir alafenamide hemifumarate can be determined by comparing *in vitro* activities, and the *in vivo* activities in animal models. Methods for the extrapolation of effective amounts / dosages in mice and other animals to therapeutically effective amounts / dosages in humans are known in the art.

[0259] The amount of tenofovir alafenamide hemifumarate required for use in treatment will vary with several factors, including but not limited to the route of administration, the nature of the condition being treated, and the age and condition of the patient; ultimately, the amount administered will be at the discretion of the attendant physician or clinician. The therapeutically effective amount / dose of tenofovir alafenamide hemifumarate depends, at least, on the nature of the condition being treated, any toxicity or drug interaction issues, whether the compound is being used prophylactically (e.g., sometimes requiring lower doses) or against an active disease or condition, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies.

[0260] In one embodiment, the oral dose of tenofovir alafenamide hemifumarate may be in the range from about 0.0001 to about 100 mg/kg body weight per day, for example, from about 0.01 to about 10 mg/kg body weight per day, from about 0.01 to about 5 mg/kg body weight per day, from about 0.5 to about 50 mg/kg body weight per day, from about 1 to about 30 mg/kg body weight per day, from about 1.5 to about 10 mg/kg body weight per day, or from about 0.05 to about 0.5 mg/kg body weight per day. As a nonlimiting example, the daily candidate dose for an adult human of about 70 kg body weight will range from about 0.1 mg to about 1000 mg, or from about 1 mg to about 1000 mg, or from about 5 mg to

about 500 mg, or from about 1 mg to about 150 mg, or from about 5 mg to about 150 mg, or from about 5 mg to about 100 mg, or about 10 mg, and may take the form of single or multiple doses. In one embodiment, the oral dose of tenofovir alafenamide hemifumarate may be in the form of a combination of agents (e.g., tenofovir alafenamide hemifumarate / emtricitabine / elvitegravir / cobicistat).

[0261] The pharmaceutical compositions described herein may further include one or more therapeutic agents in addition to tenofovir alafenamide hemifumarate. In one specific embodiment of the invention, the additional therapeutic agent can be selected from the group consisting of HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

[0262] Therapeutic methods include administering tenofovir alafenamide hemifumarate to a subject / patient in need of the same as a therapeutic or preventative treatment. Thus, tenofovir alafenamide hemifumarate may be administered to a subject / patient having a medical disorder or to a subject who may acquire the disorder. One of ordinary skill will appreciate that such treatment is given in order to ameliorate, prevent, delay, cure, and/or reduce the severity of a symptom or set of symptoms of a disorder (including a recurring disorder). The treatment may also be given to prolong the survival of a subject, e.g., beyond the survival time expected in the absence of such treatment. The medical disorders that may be treated with tenofovir alafenamide hemifumarate include those discussed herein, including without limitation, HIV infection (including, without limitation, HIV-1 and HIV-2 infections; preferably HIV-1 infection) and HBV infection.

Formulation of Cobicistat

[0263] When cobicistat or a pharmaceutically acceptable salt thereof is combined with certain specific solid carrier particles (e.g. silica derivatives), the resulting combination possesses improved physical properties. Even though cobicistat is hygroscopic in nature, the resulting combination has comparatively low hygroscopicity. Additionally, the resulting combination is a free-flowing powder,

with high loading values for cobicistat, acceptable physical and chemical stability, rapid drug release properties, and excellent compressibility. Thus, the resulting combination can readily be processed into solid dosage forms (e.g. tablets), which possess good drug release properties, low tablet friability, good chemical and physical stability, and a low amount of residual solvents. The compositions of the invention represent a significant advance that facilitates the commercial development of cobicistat for use in treating viral infections such as HIV.

[0264] Cobicistat can be combined with any suitable solid carrier, provided the resulting combination has physical properties that allow it to be more easily formulated than the parent compound. For example, suitable solid carriers include kaolin, bentonite, hectorite, colloidal magnesium-aluminum silicate, silicon dioxide, magnesium trisilicate, aluminum hydroxide, magnesium hydroxide, magnesium oxide and talc. In one embodiment of the invention, the solid carrier can comprise calcium silicate (such as ZEOPHARM), or magnesium aluminometasilicate (such as NEUSILIN). As used herein, "loaded" on a solid carrier includes, but is not limited to a compound being coated in the pores and on the surface of a solid carrier.

[0265] Suitable silica derivatives for use in the compositions of the invention and methods for preparing such silica derivatives include those that are described in international patent application publication number WO 03/037379 and the references cited therein. A specific silica material that is particularly useful in the compositions and methods of the invention is AEROPERL® 300 (fumed silica), which is available from Evonik Degussa AG, Dusseldorf, Germany. Other materials having physical and chemical properties similar to the silica materials described herein can also be used.

Ritonavir

[0266] Ritonavir (1,3-thiazol-5-ylmethyl N-[(2S,3S,5S)-3-hydroxy-5-[(2S)-3-methyl-2-{[methyl({[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl})carbamoyl]amino}butanamido]-1,6-diphenylhexan-2-yl]carbamate) was developed as an inhibitor of retroviral (HIV) protease; however, it is now used in a manner similar to cobicistat to inhibit the action of certain cytochrome P450

proteases (specifically Cyp3A4) thereby allowing greater circulating levels of drugs for treatment of HIV than would be obtained by administration of the drugs alone. Although none of GS-7340, tenofovir, or tenofovir alafenamide hemifumarate apparently is metabolized by cytochrome P450 proteases, it is contemplated that ritonavir may be used in the manner that cobicistat is used to boost the circulating levels of GS-7340, tenofovir, or tenofovir alafenamide hemifumarate, to improve the pharmacokinetics of GS-7340, tenofovir, or tenofovir alafenamide hemifumarate and achieve the other advantages of the use of cobicistat as disclosed herein.

Combination Treatment

[0267] The compounds and methods of the invention may also be used with any of the following compounds:

[0268] 1) amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, GS-8374, PPL-100, DG35, and AG 1859;

[0269] 2) an HIV nonnucleoside inhibitor of reverse transcriptase, e.g., capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirine), BILR 355 BS, VRX 840773, UK-453061, and RDEA806;

[0270] 3) an HIV nucleoside inhibitor of reverse transcriptase, e.g., zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (±-emtricitabine), D-d4FC, phosphazide, fozivudine tidoxil, apricitibine (AVX754), GS-7340, KP-1461, and fosalvudine tidoxil (formerly HDP 99.0003);

[0271] 4) an HIV nucleotide inhibitor of reverse transcriptase, e.g., tenofovir disoproxil fumarate and adefovir dipivoxil;

[0272] 5) an HIV integrase inhibitor, e.g., curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic

acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-870810, MK-0518 (raltegravir), elvitegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, and BA 011;

[0273] 6) a gp41 inhibitor, *e.g.*, enfuvirtide, sifuvirtide, FB006M, and TRI-1144;

[0274] 7) a CXCR4 inhibitor, e.g., AMD-070;

[0275] 8) an entry inhibitor, e.g., SP01A;

[0276] 9) a gp120 inhibitor, e.g., BMS-488043 or BlockAide/ CR;

[0277] 10) a G6PD and NADH-oxidase inhibitor, e.g., immunitin;

[0278] 11) a CCR5 inhibitor, e.g., aplaviroc, vicriviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

[0279] 12) other drugs for treating HIV, e.g., BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), Ampligen, HRG214, Cytolin, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040);

[0280] 13) an interferon, e.g., pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, rIFN-alpha 2a, consensus IFN alpha (infergen), feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, albuferon, locteron, Albuferon, Rebif, oral interferon alpha, IFNalpha-2b XL, AVI-005, PEG-Infergen, and pegylated IFN-beta;

[0281] 14) a ribavirin analog, e.g., rebetol, copegus, viramidine (taribavirin);

[0282] 15) an NS5b polymerase inhibitor, e.g., NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, XTL-2125, MK-0608, NM-107, R7128 (R4048), VCH-759, PF-868554, and GSK625433;

[0283] 16) an NS3 protease inhibitor, e.g., SCH-503034 (SCH-7), VX-950 (telaprevir), BILN-2065, BMS-605339, and ITMN-191;

[0284] 17) an alpha-glucosidase 1 inhibitor, e.g., MX-3253 (celgosivir), UT-231B;

[0285] 18) hepatoprotectants, e.g., IDN-6556, ME 3738, LB-84451, and MitoQ;

[0286] 19) a nonnucleoside inhibitor of HCV, e.g., benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, phenylalanine derivatives, A-831, GS-9190, and A-689; and

[0287] 20) other drugs for treating HCV, e.g., zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, NIM811, DEBIO-025, VGX-410C, EMZ-702, AVI 4065, Bavituximab, Oglufanide, and VX-497 (merimepodib).

[0288] Exemplary combinations (including, but not limited to, single tablet regimens) include (a) emtricitabine / darunavir / cobicistat / GS-7340; (b) emtricitabine / darunavir / cobicistat / tenofovir alafenamide hemifumarate; (c) emtricitabine / darunavir / cobicistat / tenofovir disoproxil fumarate (TDF); (d) emtricitabine / elvitegravir / cobicistat / GS-7340; (e) emtricitabine / elvitegravir / cobicistat / tenofovir alafenamide hemifumarate; (f) emtricitabine / elvitegravir / cobicistat / TDF; (g) cobicistat / GS-7340; (h) cobicistat / tenofovir alafenamide hemifumarate; and (i) cobicistat / TDF. The combinations listed above may contain various dosages of the component agents; as nonlimiting examples, combination (b) above can include 200 mg of emtricitabine, 800 mg of darunavir, 150 mg of cobicistat, and 10 mg of tenofovir alafenamide hemifumarate, and combination (e) above can include 200 mg of emtricitabine, 150 mg of elvitegravir, 150 mg of cobicistat, and 10 mg of tenofovir alafenamide hemifumarate.

[0289] An alternative exemplary combination is emtricitabine and tenofovir alafenamide hemifumarate. The combination of emtricitabine and TDF is currently marketed as TRUVADA®. See also U.S. Patent Application Publication No. 2004/0224916, the content of which is hereby incorporated by reference herein in its entirety. The present invention provides the combination of emtricitabine and tenofovir alafenamide hemifumarate. This combination may contain various dosages of the two component agents; as a nonlimiting example, this combination can include 200 mg of emtricitabine and 10 mg of tenofovir alafenamide hemifumarate.

[0290] An additional alternative exemplary combination is emtricitabine, rilpivirine, and tenofovir alafenamide hemifumarate. The combination of emtricitabine, rilpivirine (a nonnucleoside reverse transcriptase inhibitor), and TDF is currently marketed as COMPLERA®. The present invention provides the

combination of emtricitabine, rilpivirine, and tenofovir alafenamide hemifumarate. This combination may contain various dosages of the three component agents; as a nonlimiting example, this combination can include 200 mg of emtricitabine, 25 mg of rilpivirine, and 10 mg of tenofovir alafenamide hemifumarate.

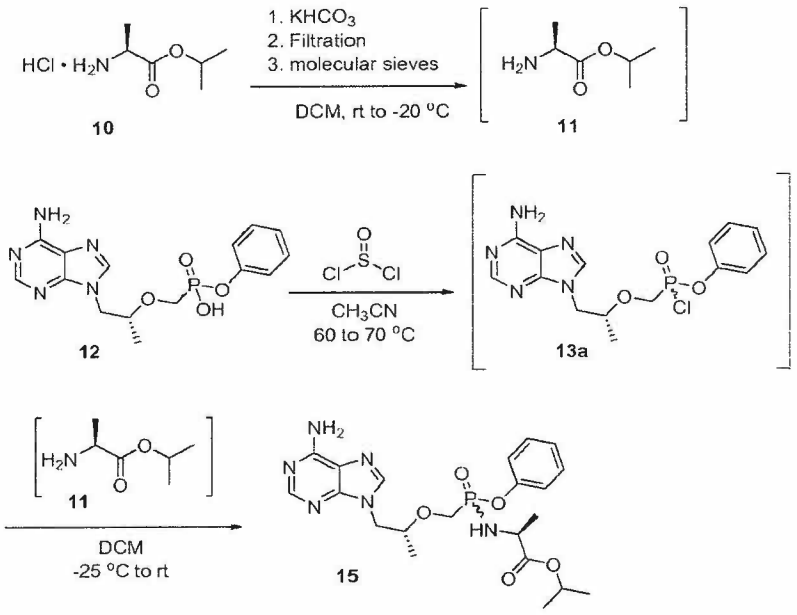
[0291] A further additional alternative exemplary combination is GS-9441 and tenofovir alafenamide hemifumarate. The combination of GS-9441 (a reverse transcriptase inhibitor) and GS-7340 is disclosed in U.S. Patent Application Publication No. 2009/0075939 and U.S. Patent No. 8,354,421, the content of each of which is hereby incorporated by reference herein in its entirety. The present invention provides the combination of GS-9441 and tenofovir alafenamide hemifumarate. This combination may contain various dosages of the two component agents; as a nonlimiting example, this combination can include 5-1500 mg of GS-9441 and 10 mg of tenofovir alafenamide hemifumarate.

[0292] Exemplary amounts of agents in various combinations include, but are not limited to, the following: (1) cobicistat: 10-500 mg, 50-500 mg, 75-300 mg, 100-200 mg, or 150 mg; (2) tenofovir alafenamide hemifumarate: 1-60 mg, 3-40 mg, 5-30 mg, 8-20 mg, or 10 mg; (3) emtricitabine: 10-500 mg, 50-500 mg, 75-300 mg, 150-250 mg, or 200 mg; (4) elvitegravir: 10-500 mg, 50-500 mg, 75-300 mg, 100-200 mg, or 150 mg; (5) darunavir: 300-1800 mg, 400-1600 mg, 500-1200 mg, 600-1000 mg, or 800 mg; and (6) rilpivirine: 5-100 mg, 10-80 mg, 15-60 mg, 20-40 mg, or 25 mg. One of skill in the art will know that, in the case of administering a pharmaceutically acceptable salt or complex of an agent, the amount administered will be adjusted relative to the weight of the component added to produce the salt or complex.

[0293] The invention will now be illustrated by the following nonlimiting Examples. The Synthetic Examples provided herein describe the synthesis of compounds of the invention as well as intermediates used to prepare compounds of the invention.

Synthetic Examples

Synthetic Example 1: Preparation of Diastereomeric Mixture of 9-[(R)-2-[[(R,S)-1-[[(S)-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine **(15)**



a. Preparation of Compound **11**

[0294] Isopropyl L-alanine ester hydrochloride **10** (1 kg, 5.97 mol, 1.0 equiv) and potassium bicarbonate (1.45 kg, 14.5 mol, 2.43 equiv) were agitated in DCM (4 kg) for 10–14 hours with maximum agitation, maintaining the pot temperature between 19 and 25 °C. The mixture was then filtered and rinsed forward with DCM (2 kg). The filtrate was dried over a bed of 4 Å molecular sieves until the water content of the solution was ≤ 0.05%. The resultant stock solution containing compound **11** was then cooled to a pot temperature of -20 °C and held for further use.

b. Preparation of Compound **13a**

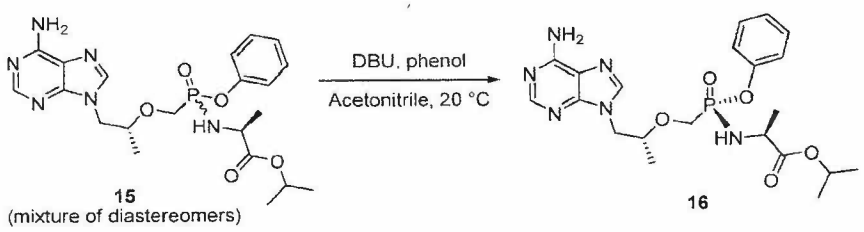
[0295] To a solution of thionyl chloride (0.72 kg, 6.02 mol, 2.19 equiv) in acetonitrile (5.5 kg) at 60 °C was added compound **12** (1 kg, 2.75 mol, 1.00 equiv) in 10 equal portions over 2 hours. The pot temperature was then adjusted to 70 °C and stirred for 1–3 hours until deemed complete by ^{31}P NMR analysis (Target: > 97.0 % conversion of starting material signal at 12.6 ppm to product signal at 22.0 ppm). The pot temperature was then adjusted to 40 °C and vacuum applied. The mixture was distilled to dryness, maintaining a maximum jacket temperature of 40 °C. The dry residue was then taken up in dichloromethane (30 kg) and the pot temperature adjusted to 19-25 °C. The resultant slurry containing compound **13a** was held for further use.

c. Preparation of Compound **15**

[0296] To the stock solution of isopropyl L-alanine ester **11** (4.82 equiv) at -25 °C was added slurry containing compound **13a** (1.0 equiv) over a minimum of 2 hours, maintaining the pot temperature ≤ -10 °C. The mixture was then held at a temperature ≤ -10 °C for at least 30 minutes, then the pH checked using water wet pH paper. If the pH was < 4, adjustment with triethylamine to pH 4–7 was performed. The pot temperature was then adjusted to room temperature (19-25 °C). In a separate vessel, a solution of sodium phosphate monobasic (2.2 kg, 18 mol, 6.90 equiv) in water (16 kg) was prepared. Half of the sodium phosphate monobasic solution was charged to the phosphonamidate reactor, and vigorously stirred. The layers were settled and partitioned. The organic layer was washed again with the remaining half of sodium phosphate monobasic solution. In a separate vessel, a solution of potassium bicarbonate (1.1 kg, 11 mol, 4.22 equiv) in water (5.5 kg) was prepared. Half of the potassium bicarbonate solution was charged to the organic phase, and vigorously stirred. The layers were settled and partitioned. The organic layer was washed again with the remaining half of the potassium bicarbonate solution followed by a final water (3.3 kg) wash. The organic phase was then retained and distilled to a volume of *ca.* 6 L. The resultant solution was analyzed for water content. If the water content was > 1.0%, DCM could be charged and the distillation to *ca.* 6 L repeated. When the solution water

content was less than or about 1.0%, the pot temperature was adjusted to 19-25 °C prior to discharge of the stock solution in DCM to provide the diastereomeric mixture of 9-[(R)-2-[[(R,S)-1-[[(S)-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine **(15)**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 – 1.33 (m, 12H), 3.62 – 3.74 (m, 1H), 3.86 – 4.22 (m, 5H), 4.30 – 4.44 (m, 1H), 4.83 – 5.10 (m, 1H), 6.02 (br s, 3H), 7.18 – 7.34 (m, 5H), 7.98 – 8.02 (m, 1H), 8.32 – 8.36 (m, 1H); ^{31}P NMR (162 MHz, $CDCl_3$): δ. 21.5, 22.9.

Synthetic Example 2: Crystallization-Induced Dynamic Resolution of Diastereomeric Mixture of 9-[(R)-2-[[(R,S)-1-[[(S)-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine **(15)** to provide 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine **(16)**



15
(mixture of diastereomers)

16

[0297] A 22 wt% solution of diastereomeric mixture of 9-[(R)-2-[[(R,S)-1-[[(S)-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine **(15)** in acetonitrile (2.3 kg solution, 0.51 kg **15**, 1.1 mol, 1 equiv) was charged to a vessel equipped with an overhead stirrer, distillation apparatus, and nitrogen inlet. The mixture was concentrated by distillation at 100-300 mbar over a temperature range of 45-55 °C to a final concentration of 30-35 wt%. The distillation apparatus was then removed and the solution was cooled to 20 °C. The solution was seeded with 2.0% compound **16** and allowed to stir for one hour at 20 °C. Phenol (9.9 g, 0.11 mol, 0.1 equiv) and DBU (16 g, 0.11 mol, 0.1 equiv) were added and the mixture was stirred for an additional 24 hours or until the weight percent of compound **16** remaining in solution was less than 12%. The slurry was then

cooled to 0 °C and stirred for an additional 18 hours at 0 °C. The slurry was filtered and washed with a 1:1 solution of isopropyl acetate:acetonitrile (1.5 L) at 0 °C. The solids were dried in a vacuum oven at 50 °C to give 0.40 kg of compound **16** (80% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (m, 9H), 1.28 (d, J = 7.0 Hz, 3H), 3.65 (dd, J= 13.1, 10.7, 1H) 4.00 (m, 4H), 4.33 (dd, J= 14.4, 3.1 Hz, 1H), 5.00 (m, 1H) 6.00 (bs, 2H), 6.99 (m, 2H), 7.07 (m, 1H), 7.19 (m, 2H), 7.97 (s, 1H), 8.33 (s, 1H). ^{31}P NMR (162 MHz, $CDCl_3$): δ. 20.8.

Synthetic Example 3: Preparation of Compound **13a** in High Diastereomeric Purity

[0298] To a slurry of compound **12** (10.0 g, 27.5 mmol, 1.00 equiv) in toluene (60 mL) at ambient temperature was added thionyl chloride (3.0 mL, 41 mmol, 1.5 equiv). The slurry was heated to 70 °C and agitated for 48–96 hours until reaction and diastereomeric enrichment were deemed complete by HPLC (Target: > 97.0 % conversion of compound **12** to compound **13a** and > 90:10 diastereomeric ratio of compound **13a**). The mixture was concentrated to dryness by vacuum distillation, and the dry residue was taken up in toluene (50 mL). The resultant slurry containing compound **13a** was held at ambient temperature for further use.

Synthetic Example 4: Preparation of 9-[(R)-2-[[(R,S)-1-[[(S)-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine **(15)** in High Diastereomeric Purity

[0299] To a solution of isopropyl L-alanine ester **11** (4.50 equiv) in DCM (80 mL) at -25 °C was added a slurry containing compound **13a** (1.00 equiv) that is at least 90% diastereomerically pure in toluene (50 mL) over a minimum of 45 minutes, maintaining the internal temperature ≤ -20 °C. The mixture was then held at a temperature ≤ -20 °C for at least 30 minutes, and the pH checked using water wet pH paper. If the pH was < 4, it was adjusted with triethylamine to pH 4-7. The pot temperature was adjusted to room temperature (19–25 °C). The mixture was transferred to a separatory funnel and washed sequentially with 10% w/v aqueous solution of sodium phosphate monobasic (2 x 50 mL), 15% w/v aqueous solution of potassium bicarbonate (2 x 20 mL), and water (50 mL). The

final organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to a viscous amber oil. The oil was dissolved in toluene / acetonitrile (4:1) (50 mL), and the solution was seeded with 9-[(R)-2-[[(R,S)-1-[[(S)-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine (about 1 mg, 99:1 diastereomeric ratio) and stirred for 2 hours at ambient temperature. The resultant slurry was filtered and the filter cake was washed with toluene / acetonitrile (4:1) (15 mL) and dried in a vacuum oven at 40 °C for 16 hours to give the product, 9-[(R)-2-[[(R,S)-1-[[(S)-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine **(15)**, as a white solid (10.0 g, 76.4%, 97.5:2.5 diastereomeric ratio). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 – 1.33 (m, 12H), 3.62 – 3.74 (m, 1H), 3.86 – 4.22 (m, 5H), 4.30 – 4.44 (m, 1H), 4.83 – 5.10 (m, 1H), 6.02 (br s, 3H), 7.18 – 7.34 (m, 5H), 7.98 – 8.02 (m, 1H), 8.32 – 8.36 (m, 1H); ^{31}P NMR (162 MHz, $CDCl_3$): δ. 21.5, 22.9.

Synthetic Example 5: Preparation of Compound **12**

[0300] PMPA (100.0 g, 0.35 mol, 1 equiv) was charged to a vessel equipped with an overhead stirrer, reflux condenser and nitrogen inlet followed by acetonitrile (800 mL). To the vessel was added triethylamine (71.0 g, 0.70 mol, 2 equiv) followed by DMAP (42.6 g, 0.35 mol, 1 equiv) and triphenylphosphite (162.1 g, 0.52 mol, 1.5 equiv). The mixture was heated to 80 °C and agitated for ≥ 48 hours at 80 °C or until the reaction was complete by ^{31}P NMR. (A sample directly from the reaction is taken and an insert containing 10% H_3PO_2 in D_2O is added. The intermediate formed is the PMPA anhydride and is at 6 ppm; the product is at 11 ppm. The reaction is deemed complete when less than 5% anhydride is present). The reaction mixture was distilled to ~1.5 volumes of acetonitrile and diluted with ethyl acetate (200 mL) and water (300 mL). The aqueous layer was separated and washed with ethyl acetate (200 mL) twice. The aqueous layer was recharged to the vessel and pH adjusted to pH 3 using 12.1 M HCl (21.0 mL). The reaction was then seeded with 0.05% of compound **12** seed and allowed to stir at 25 °C. Additional 12.1 M HCl was added over 20 minutes (7.0 mL) until pH 2 was achieved. The crystallization was allowed to stir at ambient temperature for

30 minutes and then cooled to 10°C over 2 hours. Once at 10°C the crystallization was allowed to stir for 2.5 hours at 10°C. The slurry was filtered and washed with pH 1.5 water (200 g). After drying in the vacuum oven, 102.2 g of compound **12** (81% yield) was obtained as a white solid. ^{1}H NMR (400 MHz, D_2O): δ 1.31 (d, *J*= 6.1 Hz, 3H), 3.59 (dd, *J* = 14.0, 9.0 Hz, 1H), 3.85 (dd, *J*= 14.0, 9.0 Hz, 1H), 4.1 (m, 1H), 4.3 (dd, *J*= 15.0, 9.0 Hz, 1H), 4.5 (dd, *J*= 15.0, 2 Hz, 1H), 6.75 (d, *J*= 7 Hz, 2H), 7.15 (t, *J*= 7 Hz, 1H), 7.25 (t, *J*= 7 Hz, 2H), 8.26 (s, 1H), 8.35 (s, 1H). ^{31}P NMR (162 MHz, D_2O): δ. 14.8.

Synthetic Examples – Tenofovir alafenamide hemifumarate

Synthetic Example 6

[0301] Tenofovir alafenamide monofumarate solids (5.0 g) and 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine (GS-7339) monofumarate solids (0.75 g) were charged into 35 g MTBE at 22 °C and the mixture was stirred for 1 hour. A slurry was formed and was dried in a rotary evaporator. 58 g acetonitrile (ACN) was charged into the solids and the mixture was heated to reflux to dissolve the solids. The resulting solution was allowed to cool naturally while agitated. A slurry was formed, and the slurry was further cooled by an ice-water bath. The solids were isolated by filtration and washed with 5 g ACN. The solids were dried in a vacuum oven at 40 °C overnight. 5.52 g off-white solids were obtained. The solids were analyzed by XRPD and found to contain tenofovir alafenamide monofumarate, GS-7339 monofumarate, and tenofovir alafenamide hemifumarate.

Synthetic Example 7: Preparation of Tenofovir Alafenamide Hemifumarate via Selective Crystallization

[0302] 9-[(R)-2-[[[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine as a slurry in ACN (9.7 kg slurry, 13.8 wt%, a diastereomeric mixture of 1.0 kg (2.10 mol, 1 mol equiv) of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine

and 0.35 kg of 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine was charged into a reactor and rinsed forward with dichloromethane (5 kg). The mixture was concentrated under vacuum to about 3 L with jacket temperature below 40 °C. The concentrate was then coevaporated with ACN (6 kg) under vacuum to about 3 L with jacket temperature below 40 °C. The concentrate was diluted with ACN (8.5 kg) and warmed to 40-46 °C. The warm mixture was filtered into a second reactor and the filtrate was cooled to 19-25 °C.

[0303] To the above solution was charged fumaric acid (0.13 kg, 1.12 mol, 0.542 mole equiv) followed by ACN (1 kg), and the mixture was heated to 67-73 °C. The hot mixture was transferred into a reactor via a polishing filter, and then adjusted to 54-60 °C. Seed crystals (5 g) of the hemifumarate form of tenofovir alafenamide were charged (for example, the mixture can be seeded with tenofovir alafenamide hemifumarate formed in Synthetic Example 6 or a subsequent production), and the resulting mixture was agitated at 54-60 °C for about 30 minutes. The mixture was cooled over a minimum of 4 hours to 0-6 °C, and then agitated at 0-6 °C for a minimum of 1 hour. The resulting slurry was filtered and rinsed with chilled (0-6 °C) ACN (2 kg). The product was dried under vacuum below 45 °C until loss on drying (LOD) and organic volatile impurities (OVI) limits were met (LOD ≤ 1.0%, dichloromethane content ≤ 0.19%, acetonitrile content ≤ 0.19%) to afford the final compound of the hemifumarate form of tenofovir alafenamide as a white to off-white powder (typical yield is about 0.95 kg). ^{1}H NMR (400 MHz, d6 DMSO): δ 1.06 (d, J = 5.6 Hz, 3H), 1.12-1.16 (m, 9H), 3.77 (dd, J = 10.4, 11.6 Hz, 1H), 3.84-3.90 (m, 2H), 3.94 (m, 1H), 4.14 (dd, J = 6.8, 14.8 Hz, 1H), 4.27 (m, 1H), 4.85 (heptet, J = 6.0 Hz, 1H), 5.65 (t, J = 11.2 Hz, 1H), 6.63 (s, 1H), 7.05 (d, J = 7.6 Hz, 2H), 7.13 (t, J = 7.2 Hz, 1H), 7.24 (s, 2H), 7.29 (t, J = 7.6 Hz, 2H), 8.13 (t, J = 13.6 Hz, 2H), ^{31}P NMR (162 MHz, d6 DMSO): δ 23.3.

Synthetic Example 8: Preparation of Tenofovir Alafenamide Hemifumarate

[0304] To a jacketed reactor equipped with overhead agitator, was charged 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine

(10 g), fumaric acid (1.22 g), and ACN (100 mL). The mixture was heated to 70-75 °C to dissolve the solids. Any undissolved particulates were removed by filtration through a cartridge filter. The filtered solution was cooled to 60-65 °C, and seeded with 1% (by weight) of tenofovir alafenamide hemifumarate. The slurry was aged for 30 minutes and cooled to 0-5 °C over 2 hours. The temperature was maintained for 1-18 hours, and the resulting slurry was filtered and washed with 2 ml of cold ACN (0-5 °C). The solids were dried under vacuum at 50 °C to provide the hemifumarate form of tenofovir alafenamide, which was characterized as described below.

Characterization of Tenofovir Alafenamide Hemifumarate from Synthetic Example 8

[0305] Tenofovir alafenamide hemifumarate from Synthetic Example 8 consists of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine and one-half an equivalent of fumaric acid. Tenofovir alafenamide hemifumarate is anhydrous, nonhygroscopic, and has a DSC onset endotherm of about 131 °C.

X-ray Powder Diffraction

[0306] The XRPD pattern of tenofovir alafenamide hemifumarate was obtained in the following experimental setting: 45 KV, 45 mA, Kα1=1.5406 Å, scan range 2. - 40°, step size 0.0084°, counting time: 8.25 s. The XRPD pattern for tenofovir alafenamide hemifumarate is shown in Figure 13. The characteristic peaks include: 6.9 ± 0.2°, 8.6 ± 0.2°, 10.0 ± 0.2°, 11.0 ± 0.2°, 12.2 ± 0.2°, 15.9 ± 0.2°, 16.3 ± 0.2°, 20.2 ± 0.2°, and 20.8 ± 0.2°.

Single-Crystal X-ray Diffraction

[0307] The crystal size was 0.32 x 0.30 x 0.20 mm^3. The sample was held at 123 K and the data was collected using a radiation source with a wavelength of 0.71073 Å in the theta range of 1.59 to 25.39°. Conditions of, and data collected from the single-crystal X-ray diffraction are shown in Table 1.

Table 1. Single-Crystal X-ray Diffraction

Empirical formula	$C_{23}H_{31}N_6O_7P$
Formula weight	534.50
Temperature	123(2) K
Crystal size	0.32 x 0.30 x 0.20 mm^3
Theta range for data collection	1.59 to 25.39°
Wavelength	0.71073 Å
Crystal system	Tetragonal
Space group	P4(2)2(1)2
Unit cell dimensions	a = 18.1185(12) Å α = 90° b = 18.1185(12) Å β = 90° c = 17.5747(11) Å γ = 90°
Volume	5769.4(6) $Å^3$
Z	8
Density (calculated)	1.231 g/cm^3

DSC Analysis

[0308] The DSC analysis was conducted using 2.517 mg of tenofovir alafenamide hemifumarate. It was heated at 10 °C/min over the range of 40-200 °C. The onset endotherm was found to be about 131 °C (Figure 14).

TGA Data

[0309] The TGA data were obtained using 4.161 mg of tenofovir alafenamide hemifumarate. It was heated at 10 °C/min over the range of 25-200 °C. The sample lost 0.3% weight before melting (Figure 15). It was determined to be an anhydrous form.

DVS Analysis

[0310] DVS analysis was conducted using 4.951 mg of tenofovir alafenamide hemifumarate. The material was kept at 25 °C in nitrogen at humidities ranging from 10% to 90% relative humidity; each step was equilibrated for 120 minutes.

The sorption isotherm is shown at Figure 16. The material was found to be nonhygroscopic, and to absorb 0.65% water at a relative humidity of 90%.

Purging of Diastereomeric Impurity

[0311] In the prior syntheses of tenofovir alafenamide, one of the major impurities is typically the diastereomer 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine. The hemifumarate form of tenofovir alafenamide from Synthetic Example 8 has an exceptional capability to purge this diastereomeric impurity, as compared with the capability of the monofumarate form (described in, e.g., U.S. Patent No. 7,390,791). The data in Table 2 (below) demonstrates that tenofovir alafenamide hemifumarate (Batch 2) purged the diastereomeric impurity to less than one-tenth of the starting concentration, whereas the monofumarate form of tenofovir alafenamide (Batch 1) only slightly purged the diastereomeric impurity.

Table 2. Purging Capability Comparison

Batch	Diastereomeric Impurity in Starting Material	Solvent	Fumaric acid charge (mole equivalent)	Product obtained	Diastereomeric Impurity in Product
1	9.3%	ACN	0.9	Monofumarate form	7.6%
2	10.0%	ACN	0.5	Hemifumarate form	0.65%

Chemical Stability

[0312] Chemical stability of the hemifumarate form of tenofovir alafenamide was compared with the monofumarate form. As shown in Table 3 (below), under identical conditions, the hemifumarate form of tenofovir alafenamide was chemically more stable and exhibited better long-term storage stability, with significantly less degradation (% Total Deg. Products) than the monofumarate form. Conditions evaluated include temperature, relative humidity (RH), and the open or closed state of the container cap.

Table 3. Chemical Stability Comparison

Storage Condition	Time Points (weeks)	Monofumarate form		Hemifumarate form	
		% TA* Area Normalized	% Total Deg. Products	% TA Area Normalized	% Total Deg. Products
40°C / 75% RH Cap Closed	0	97.1	0.69	98.4	0.05
	1	97.0	0.87	98.4	0.14
	2	96.6	1.18	98.5	0.14
	4	96.4	1.49	98.4	0.25
	8	95.4	2.36	98.0	0.49
40°C / 75% RH Cap Open	0	97.1	0.69	98.4	0.05
	1	96.9	0.90	98.5	0.15
	2	96.6	1.10	98.5	0.14
	4	96.2	1.67	98.4	0.26
	8	95.0	2.74	98.1	0.50
70°C Cap Closed	0	97.1	0.69	98.4	0.05
	2	96.2	1.83	98.5	0.22
	4	93.3	4.78	98.4	0.33

*TA is tenofovir alafenamide

Thermodynamic Stability

[0313] Stable form screening of tenofovir alafenamide hemifumarate showed that it is thermodynamically stable in most solvents, such as ACN, toluene, ethyl acetate, methyl *tert*-butyl ether (MTBE), acetone, THF, and 2-methyl THF. A similar stable form screening of the monofumarate form showed that this form is not thermodynamically stable in the above-listed solvents. When suspended in these solvents, the monofumarate form of tenofovir alafenamide fully converts to the hemifumarate form in THF and 2-methyl THF, and partially converts to the hemifumarate form in ACN, ethyl acetate, MTBE, and acetone, as well as at ambient temperatures.

Thermal Stability

[0314] As shown by the DSC data, the hemifumarate form of tenofovir alafenamide has a melting point that is about 10 °C higher than that of the monofumarate form, indicating that the hemifumarate form has improved thermal stability as compared with the monofumarate form.

Biological Example 1: Transport Studies

[0315] Caco-2 transepithelial transport studies: Caco-2 cells between passage 43 and 69 were grown to confluence over at least 21 days on 24-well polyethylene-terephthalate (PET) transwell plates (BD Biosciences, Bedford, MA). Experiments were conducted using Hank's Buffered Salt Solution (HBSS) containing 10 mM HEPES and 15 mM Glucose obtained from Life Technologies (Grand Island, NY). Donor and receiver buffers had their pH adjusted to pH 6.5 and 7.4, respectively. The receiver well used HBSS buffer supplemented with 1% bovine serum albumin. In studies done to determine transport inhibition, monolayers were preincubated for 60 minutes in the presence of assay buffer and inhibitor in order to saturate any transporter binding sites. Following preincubation, fresh assay buffer containing inhibitor and the test compound were added. Test compound concentrations in assay chambers were analyzed by liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS). Transepithelial electrical resistance (TEER) and lucifer yellow permeability were determined to assure membrane integrity. Each individual experiment was done in duplicate and the permeation of control compounds atenolol (low permeability), propranolol (high permeability), and vinblastine (efflux transport) were determined to meet acceptance criteria for each batch of assay plates.

[0316] Pgp and BCRP inhibition assays in transfected Madin-Darby canine kidney (MDCKII) cells: Inhibition of Pgp-mediated transport was studied using the Pgp substrate calcein AM and MDCKII cells transfected with the human MDR1 (ABCB1) gene (encoding Pgp). Similarly, inhibition of BCRP-mediated transport was studied using the BCRP substrate Hoechst 33342 and MDCKII cells transfected with the human ABCG2 gene (encoding BCRP). Briefly, MDCKII cells were seeded in 96-well black cell culture plates with clear bottoms at a density of 5×10^4 cells/well and grown to confluence overnight. Test compounds were diluted in cell culture medium containing 10 μM Hoechst 33342 and incubated for 3 hours with MDCKII-BCRP and nontransfected cells. Following removal of media containing Hoechst 33342 and test compound, cells were washed twice with warm medium and lysed at room temperature for 5-10 minutes in a buffer containing 20 mM Tris-HCl pH 9.0 and 0.4% Triton X-100. Wells were

analyzed for Hoechst 33342 fluorescence at an excitation of 353 nm and an emission of 460 nm.

[0317] Pgp and BCRP substrate assays in transfected MDCKII cells: MDCKII cells were grown to confluence over 4-6 days on 24-well PET transwell plates (BD Biosciences). The same buffers were used in the donor and receiver wells as described above for caco-2 studies. Experiments were conducted as described above for caco-2 transepithelial transport studies and samples analyzed by LC/MS/MS. Similar quality control and acceptance criteria were used as those described above for caco-2 studies. TEER values and the permeability of lucifer yellow, atenolol, and propranolol were determined to meet acceptance criteria for each batch of assay plates. Efflux ratios were determined to be at least 3-fold higher in transfected versus nontransfected monolayers for the model Pgp substrate vinblastine and BCRP substrate prazosin.

[0318] Data analysis: The 50% inhibition constants (IC_{50}) values for transporters in the fluorescent accumulation studies done in MDCKII cells, defined as the test article concentration needed to inhibit the maximal transporter specific transport by 50%, were calculated using nonlinear curve fitting of inhibition versus concentration to a sigmoidal curve with a variable Hill coefficient using GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA). Apparent permeability coefficients and efflux ratios (ER) from transcellular experiments in caco-2 or MDCKII cells were calculated as previously described (Tong et al. (2007) *Antimicrob Agents Chemother* 51:3498-504). Where appropriate, the statistical significance of differences observed between test conditions was assessed using paired two-tailed Student's *t* tests.

[0319] Inhibition of Pgp and BCRP in transfected MDCKII cells: The inhibition of Pgp and BCRP by cobicistat relative to ritonavir and the known transport inhibitors cyclosporin A (CSA) and fumitremorgin C was studied by monitoring the effects of coincubation on the Pgp- and BCRP-dependent accumulation of the fluorescent probe substrates calcein AM and Hoechst 33342 in MDCKII-MDR1 and MDCKII-ABCG2 cells, respectively. Cobicistat inhibited Pgp and BCRP with IC_{50} values of 36 ± 10 μM and 59 ± 28 μM, respectively. Ritonavir, when incubated at its approximate solubility limit in assay buffers (20 μM) showed 35%

inhibition of Pgp and 21% inhibition of BCRP. Higher concentrations of cobicistat were achievable in assays because of its > 35-fold higher aqueous solubility at neutral pH. Greater differences in the concentrations of cobicistat and ritonavir may exist in the gastrointestinal (GI) tract based on their respective solubility under acidic conditions. Taken together, the solubility and inhibition results indicate that cobicistat should have similar inhibition of Pgp and BCRP in the GI tract relative to ritonavir.

[0320] Pgp and BCRP substrate assays in transfected MDCKII cells: To further characterize the mechanism interaction of cobicistat with Pgp (multidrug resistance protein 1; MDR1) and BCRP, bidirectional permeability assays were completed in cells transfected with the genes for the human transport proteins to determine if cobicistat is a substrate for these efflux transporters (Figure 10). Bidirectional permeability of cobicistat (10 μM) was assessed in MDCKII-WT, MDCKII-MDR1 (Figure 10A) and MDCKII-BCRP cells (Figure 10B). The black bars show apical to basolateral (A-B) permeability, and the open bars show basolateral to apical (B-A) permeability. Efflux ratios are indicated above graphs for each experimental condition. CSA (10 μM) and Ko134 (10 μM) were used as known inhibitors of Pgp and BCRP, respectively. Results are the average of duplicate wells from a representative side by side experiment done comparing wild type MDCKII (MDCKII-WT) to MDCKII-MDR1 or MDCKII-BCRP cells in the presence or absence of respective inhibitors. The overexpression of Pgp or BCRP in MDCKII cells increased the efflux ratios of cobicistat. These increased efflux ratios reflected a decrease in the forward permeability and an increase in the reverse permeability of cobicistat. Consistent with Pgp- and BCRP-dependent transport, cobicistat efflux was decreased in the presence of the Pgp inhibitor CSA and the BCRP inhibitor Ko134. These results illustrate that cobicistat is a substrate for both Pgp and BCRP, suggesting that the observed inhibition may be due to competition for the binding sites of the respective transporters.

[0321] Effect of cobicistat on the bidirectional permeability of model Pgp and BCRP substrates through caco-2 cell monolayers: Caco-2 cells have been reported as a physiologically relevant model system of GI absorption that supports the polarized expression of intestinal transporters including Pgp and BCRP. The effect

of cobicistat (COBI; 90 μM) and ritonavir (RTV; 20 μM) on the bidirectional permeability through monolayers of caco-2 cells of 10 μM of the Pgp substrate digoxin (Figure 11A) and BCRP substrate prazosin (Figure 11B) were studied. Digoxin and prazosin were chosen as model substrates of Pgp and BCRP, respectively, based on recommendations from the FDA and by the International Transporter Consortium. The known Pgp inhibitor CSA (10 μM) and BCRP inhibitor fumitremorgin C (2 μM; noted in Figure 11B as "FTC") were used as positive controls. The black bars show apical to basolateral (A-B) and the open bars basolateral to apical (B-A) permeability, and efflux ratios are indicated above graphs for each experimental condition. Results are the mean ± standard deviation of at least four independent experiments done in duplicate, and statistical significance was assessed by comparing results to no cotreatment wells using paired two-tailed Student's *t* tests (*, $P < 0.05$; **, $P < 0.01$). Similar to the known Pgp inhibitor CSA, cobicistat and ritonavir markedly reduced the efflux ratio and significantly increased the apical to basolateral (A-B) permeability of digoxin (Figure 11A). Similar effects were observed in experiments studying the effect of cobicistat and ritonavir relative to the known BCRP inhibitor fumitremorgin C on the permeability of the BCRP substrate prazosin (Figure 11B). These data suggest similar inhibitory effects of cobicistat and ritonavir on the Pgp-mediated transport of digoxin- and BCRP-mediated transport of prazosin.

[0322] Effect of cobicistat on the bidirectional permeability of HIV protease inhibitors and GS-7340 through caco-2 cell monolayers: The effect of cobicistat (90 μM) and ritonavir (20 μM) on the bidirectional permeability of the HIV protease inhibitors (PIs) atazanavir, darunavir, lopinavir, and GS-8374, an experimental HIV PI, through caco-2 cell monolayers was assessed. The effect of RTV and COBI was assessed with 10 μM of the HIV PIs atazanavir (Figure 12A), darunavir (Figure 12B), lopinavir (Figure 12C) and GS-8374 (Figure 12D). The black bars show apical to basolateral (A-B) and the open bars basolateral to apical (B-A) permeability, and efflux ratios are indicated above graphs for each experimental condition. Results are the mean ± standard deviation of at least four independent experiments done in duplicate, and statistical significance was assessed comparing directional results to no cotreatment wells by using paired two-

tailed Student's *t* tests (*, P <0.05; **, P<0.01; ***,P<0.001). The effect of COBI (90 μM) was assessed on the bidirection permeability of GS-7340 (10 μM) through caco-2 monolayers over a 2 hour time course in the A-B (Figure 12E) and B-A (Figure 12F) directions. Open symbols depict presence and solid symbols depict absence of COBI. Results are the mean ± standard deviation of duplicate measurements from two independent experiments. Consistent with previous studies reporting these compounds as Pgp substrates, significant efflux was observed for each of the protease inhibitors. Coadministration of cobicistat and ritonavir comparably reduced the efflux ratios by increasing the A-B flux and decreasing the B-A flux of the protease inhibitors (Figure 12A-D). The effect of cobicistat on GS-7340 permeability across caco-2 monolayers was monitored over 2 hours, and cobicistat increased the A-B flux of GS-7340 while concomitantly reducing B-A flux (Figure 12E-F).

[0323] These results support the hypothesis that cobicistat may be acting to inhibit Pgp-mediated intestinal secretion of GS-7340.

Biological Example 2

[0324] Pharmacokinetic studies were done in humans to determine exposure to GS-7340 at three dose levels. Eligible subjects were randomized to receive either GS-7340 dose of 8 mg, GS-7340 dose of 25 mg, GS-7340 dose of 40 mg, tenofovir (as TDF) 300 mg or placebo-to-match GS-7340 for 10 days. (Note: Doses of GS-7340 are given as the mass of free base of GS-7340, even where other forms of GS-7340 were dosed.) GS-7340 was administered in a blinded fashion, unless a subject was randomized to receive tenofovir which was given on an open-label basis.

[0325] Figure 1 shows tenofovir plasma concentrations in patients on Day 1 of the study. The top line (no symbol) shows the concentration of tenofovir in patients dosed with 300 mg tenofovir (as TDF). The next line down (triangles pointed down) shows the concentration of tenofovir in patients dosed with 40 mg GS-7340. The next line down (triangles pointed up) shows the concentration of tenofovir in patients dosed with 25 mg GS-7340. The bottom line (squares) shows the

concentration of tenofovir in patients dosed with 8 mg GS-7340. The table below the graph shows Cmax and AUC values obtained.

[0326] Figure 2 shows tenofovir plasma concentrations in patients on Day 10 of the study. The top line (diamonds) shows the concentration of tenofovir in patients dosed with 300 mg tenofovir. The next line down (triangles pointed down) shows the concentration of tenofovir in patients dosed with 40 mg GS-7340. The next line down (triangles pointed up) shows the concentration of tenofovir in patients dosed with 25 mg GS-7340. The bottom line (squares) shows the concentration of tenofovir in patients dosed with 8 mg GS-7340. The table below the graph shows Cmax and AUC values obtained.

Biological Example 3

[0327] Drug interaction potential between once-daily emtricitabine (FTC) / GS-7340 fixed dose combination, cobicistat boosted darunavir plus GS-7340 as a single agent, and efavirenz or cobicistat-boosted darunavir was evaluated in an open-label, crossover, single-center, multiple-dose, multiple-cohort study.

[0328] Table 4 shows the dosing regimen and schedule for the study.

Cohort 1 (n = 12)		
Cohort	Day 1–12	Day 13–26
	Treatment A: FTC/GS-7340 FDC (200/40 mg) administered once-daily in the morning under fasted condition	**Treatment B:** FTC/GS-7340 FDC (200/40 mg) plus efavirenz (EFV) 600 mg administered once-daily in the morning under fasted condition
Cohort 2 (n = 12)		
Cohort	Day 1–12	Day 13–22
	Treatment C: FTC/GS-7340 FDC (200/25 mg) administered once-daily in the morning under fed condition	**Treatment D:** FTC/GS-7340 FDC (200/25 mg) plus cobicistat-boosted darunavir (DRV/co; 800/150 mg) administered once-daily in the morning under fed condition
Cohort 3 (n = 14)		
Cohort	Day 1–10	Day 11–22
	Treatment E: Cobicistat boosted darunavir (DRV/co; 800/150 mg) administered once-daily in the morning under fed condition	**Treatment F:** FTC/GS-7340 FDC (200/25 mg) plus cobicistat boosted darunavir (DRV/co, 800/150 mg) administered once daily in the morning under fed condition
Cohort 4 (n = 12):		
Cohort	Day 1–12	Day 13–22
	Treatment G: GS-7340 (8 mg) single agent administered once daily in the morning under fed conditions	**Treatment H:** GS-7340 (8 mg) single agent PLUS cobicistat (150 mg) administered once daily in the morning under fed Conditions

Table 4

[0329] Results of the pharmacokinetic analysis in this study are shown in Figures 3-5. (Note: Doses of GS-7340 are given as the mass of free base of GS-7340, even where other forms of GS-7340 were dosed.)

[0330] Figure 3A shows GS-7340 (tenofovir alafenamide) concentrations (ng/ml) for doses of emtricitabine and GS-7340 (triangles pointed up) and emtricitabine, GS-7340 and efavirenz ((initial value = 100 ng/ml); triangles pointed down) in patients from Cohort 1. Cmax and AUC results are displayed in the table below for GS-7340 exposure. Tenofovir (TFV) concentrations are shown in Figure 3B for doses of emtricitabine and GS-7340 (upper line; triangles pointed up) and emtricitabine, GS-7340 and efavirenz (lower line: triangles pointed down). Cmax and AUC results are displayed in the table below for tenofovir exposure.

[0331] Figure 4A shows GS-7340 concentrations (ng/ml) for doses of emtricitabine and GS-7340 (triangles pointed up) and emtricitabine, GS-7340, darunavir, and cobicistat (triangles pointed down) in patients from Cohort 2. C_{max} and AUC results are displayed in the table below for GS-7340 exposure. Tenofovir (TFV) concentrations are shown in Figure 4B for doses of emtricitabine and GS-7340 (triangles pointed up) and emtricitabine, GS-7340, darunavir, and cobicistat (triangles pointed down). C_{max} and AUC results are displayed in the table below for tenofovir exposure.

[0332] Figure 5A shows GS-7340 concentrations (ng/ml) for doses of GS-7340 alone and GS-7340 and cobicistat (triangles pointed up). C_{max} and AUC results are displayed in the table below for GS-7340 exposure. Tenofovir (TFV) concentrations are shown in Figure 5B for doses of GS-7340 alone (triangles pointed up) and GS-7340 and cobicistat (triangles pointed down). C_{max} and AUC results are displayed in the table below for tenofovir exposure.

[0333] Increases in exposures were observed for GS-7340 (tenofovir alafenamide) and TFV when dosed as GS-7340 (8 mg) plus COBI (150 mg) versus GS-7340 (8 mg) as a stand-alone agent. GS-7340 AUC_{last} and C_{max} were ~2.7- and 2.8-fold higher, respectively, whereas TFV AUC_{tau} and C_{max} were ~3.3- and 3.3-fold higher, respectively. These data suggest that the interaction is COBI-mediated, likely due to inhibition of Pgp-mediated intestinal secretion of tenofovir alafenamide (GS-7340).

Biological Example 4

[0334] GS-7340 and cobicistat were administered in conjunction with elvitegravir and emtricitabine in a clinical trial to determine the relative bioavailability of these compounds. The compounds were administered using a 25 mg or 40 mg dose of GS-7340 (test) relative to exposures (elvitegravir, cobicistat, emtricitabine) from elvitegravir/cobicistat/emtricitabine/tenofovir (reference) or GS-7340 (TFV) (reference). A second cohort with a similar design evaluated an alternate formulation of elvitegravir/cobicistat/emtricitabine/GS-7340 STR. (Note: Doses of Compound are given as the mass of free base of GS-7340, even where other forms of GS-7340 were dosed.) Elvitegravir/cobicistat/emtricitabine/GS-7340 (monolayer) tablets were manufactured by blending of emtricitabine/GS-7340 granulation with elvitegravir granulation and cobicistat, tablet compression, tablet film-coating, and packaging. Elvitegravir/cobicistat/emtricitabine/GS-7340 bilayer tablets are manufactured by compression of the elvitegravir/cobicistat layer and emtricitabine/GS-7340 layer, tablet film-coating, and packaging. In order to provide a robust assessment of pharmacokinetic comparisons between test versus reference treatments, a balanced Williams 4 x 4 design was used in each cohort.

[0335] The dose of elvitegravir (150 mg), the boosting dose of cobicistat (150 mg), and dosage of emtricitabine (200 mg) in elvitegravir/cobicistat/emtricitabine/GS-7340 represent current investigational doses (elvitegravir, cobicistat) or marketed dose (emtricitabine) with demonstrated durable efficacy and long-term safety in HIV-infected patients.

[0336] The evaluation used two cohorts of twenty patients. In Cohort 1, the following study treatments were administered.

[0337] **Treatment A:** 1 × Single Tablet Regimen (STR) of **Formulation 1** (150 mg elvitegravir plus 150 mg cobicistat plus 200 mg emtricitabine plus 25 mg GS-7340 (as 31.1 mg of the fumarate salt GS-7340-02)) QD, administered in A.M. for 12 days.

[0338] **Treatment B:** 1 × STR **Formulation 1** (150 mg elvitegravir plus 150 mg cobicistat plus 200 mg emtricitabine plus 40 mg GS-7340 (as 49.7 mg of the fumarate salt GS-7340-02)) QD, administered in A.M. for 12 days.

[0339] Treatment C: 1 × STR (150 mg elvitegravir plus 150 mg cobicistat plus 200 mg emtricitabine plus 300 mg tenofovir (as tenofovir disoproxil fumarate) QD, administered in A.M. for 12 days.

[0340] Treatment D: 1 × 25 mg GS-7340 tablet QD, administered in A.M. for 12 days.

[0341] Patients were randomized to one of four sequences (I, II, III, or IV).

	Day 1-12	Day 15-26	Day 29-40	Day 43-54
Sequence I	A	B	C	D
Sequence II	B	D	A	C
Sequence III	C	A	D	B
Sequence IV	D	C	B	A

[0342] Formulation 1 (monolayer) was prepared by blending of emtricitabine/GS-7340 granulation with elvitegravir granulation and cobicistat, tablet compression, tablet film-coating, and packaging. The EVG/COBI/FTC/GS-7340 STR tablet cores contain colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, microcrystalline cellulose, sodium lauryl sulfate, and magnesium stearate as inactive ingredients and are film-coated with polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide.

[0343] In Cohort 2, the following study treatments were administered:

[0344] Treatment E: 1 × STR **Formulation 2** (150 mg elvitegravir plus 150 mg cobicistat plus 200 mg emtricitabine plus 25 mg GS-7340 (as 31.1 mg of the fumarate salt GS-7340-02)) QD, administered in A.M. for 12 days.

[0345] Treatment F: 1 × STR **Formulation 2** (150 mg elvitegravir plus 150 mg cobicistat plus 200 mg emtricitabine plus 40 mg GS-7340 (as 49.7 mg of the fumarate salt GS-7340-02)) QD, administered in A.M. for 12 days.

[0346] Treatment C: 1 × STR (150 mg elvitegravir plus 150 mg cobicistat plus 200 mg emtricitabine plus 300 mg tenofovir) QD, administered in A.M. for 12 days.

[0347] Treatment D: 1 × 25 mg GS-7340 tablet QD, administered in A.M. for 12 days.

[0348] Patients were randomized to one of four sequences (I, II, III, or IV).

	Day 1-12	Day 15-26	Day 29-40	Day 43-54
Sequence I	E	F	C	D
Sequence II	F	D	E	C
Sequence III	C	E	D	F
Sequence IV	D	C	F	E

[0349] Formulation 2 was prepared as bilayer tablets that were manufactured by compression of the elvitegravir/cobicistat layer and emtricitabine/GS-7340 layer, tablet film-coating, and packaging. The EVG/COBI/FTC/GS-7340 STR tablet cores contain colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, microcrystalline cellulose, sodium lauryl sulfate, and magnesium stearate as inactive ingredients and are film-coated with polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide.

[0350] Figure 6 shows pharmacokinetic data for GS-7340 from patients treated in Cohort 1 (Formulation 1, monolayer). The top line (triangles pointed down) shows GS-7340 concentration (ng/ml) when 40 mg GS-7340 is administered with cobicistat. The middle line (triangles pointed up) shows GS-7340 concentration (ng/ml) when 25 mg GS-7340 is administered with cobicistat. The bottom line (squares) shows GS-7340 concentration (ng/ml) when 25 mg GS-7340 is administered alone. These results show GS-7340 levels that are 2.2-fold higher for dosing at the 25 mg level when GS-7340 is administered with cobicistat.

[0351] Figure 7 shows pharmacokinetic data for GS-7340 from patients treated in Cohort 2 (Formulation 2, bilayer). The top line (triangles pointed down) shows GS-7340 concentration (ng/ml) when 40 mg GS-7340 is administered with cobicistat. The middle line (triangles pointed up) shows GS-7340 concentration (ng/ml) when 25 mg GS-7340 is administered with cobicistat. The bottom line (squares) shows GS-7340 concentration (ng/ml) when 25 mg GS-7340 is administered alone. These results also show GS-7340 levels that are 2.2-fold higher for dosing at the 25 mg level when GS-7340 is administered with cobicistat.

[0352] Figure 8 shows pharmacokinetic data for tenofovir from patients treated in Cohort 1 (Formulation 1, monolayer). The top line (no symbol) shows tenofovir concentration (ng/ml) when 300 mg tenofovir is administered with cobicistat. The

next line down (triangles pointed up) shows tenofovir concentration (ng/ml) when 40 mg GS-7340 is administered with cobicistat. The next line down (squares) shows tenofovir concentration (ng/ml) when 25 mg GS-7340 is administered with cobicistat. The bottom line (triangles pointed down) shows tenofovir concentration (ng/ml) when 25 mg GS-7340 is administered alone. These results also show tenofovir levels that are 3-4 fold higher for dosing at the 25 mg level when tenofovir or GS-7340 is administered with cobicistat.

[0353] Figure 9 shows pharmacokinetic data for tenofovir from patients treated in Cohort 2 (Formulation 2, bilayer). The top line (circles) shows tenofovir concentration (ng/ml) when 300 mg tenofovir is administered with cobicistat. The next line down (triangles pointed up) shows tenofovir concentration (ng/ml) when 40 mg GS-7340 is administered with cobicistat. The next line down (squares) shows tenofovir concentration (ng/ml) when 25 mg GS-7340 is administered with cobicistat. The bottom line (triangles pointed down) shows tenofovir concentration (ng/ml) when 25 mg GS-7340 is administered alone. These results also show GS-7340 levels that are 3-4 fold higher for dosing at the 25 mg level when tenofovir or GS-7340 is administered with cobicistat.

[0354] Following administration of EVG/COBI/FTC/GS-7340 (25 mg) Formulations 1 and 2, geometric mean GS-7340 and TFV exposures were substantially higher, relative to GS-7340 (25 mg) as a stand-alone agent. With both formulations of EVG/COBI/FTC/GS-7340 (25 mg), GS-7340 AUC_{last} and C_{max} were ~2.2- and 2.3-fold higher, respectively, whereas TFV AUC_{tau} and C_{max} were ~3.1- and 3.7-fold higher, respectively. GS-7340 and TFV exposures were generally dose-proportional following EVG/COBI/FTC/GS-7340 (40 mg) versus EVG/COBI/FTC/GS-7340 (25 mg).

Biological Example 5

[0355] GS-7340 was coformulated with elvitegravir (EVG), cobicistat (COBI), and emtricitabine (FTC) into a single tablet regimen (STR). Across three healthy subject studies, the multiple dose pharmacokinetics (PK) of EVG/COBI/FTC/GS-7340 STR and/or interaction potential between GS-7340 and

COBI were evaluated to facilitate GS-7340 dose selection for STR clinical development.

[0356] In Study 1 (n=20), subjects received EVG/COBI/FTC/GS-7340 (150/150/200/40 or 150/150/200/25 mg), EVG/COBI/FTC/TDF (150/150/200/300 mg) or GS-7340 25 mg stand alone (SA), 12 days/treatment in a balanced Williams 4 x 4 design. In Study 2 (n=12), subjects sequentially received GS-7340 (8 mg) SA (Reference) for 12 days and GS-7340 plus COBI (8/150 mg) (Test) for 10 days. In Study 3 (n=34), across two cohorts (each 2 x 2 crossover design), subjects received EVG/COBI/FTC/GS-7340 (150/150/200/10 mg) (Test, both cohorts), EVG plus COBI (150/150 mg) (Reference, Cohort 1), and FTC plus GS-7340 (200/25 mg) (Reference, Cohort 2), each treatment dosed for 12 days. Statistical comparisons of GS-7340 and TFV were made using geometric mean ratios (GMR), with 90% confidence intervals (CI) of 70-143% (Study 1: Test = EVG/COBI/FTC/GS-7340, Reference = GS-7340 SA). Safety assessments were performed throughout dosing and follow up.

[0357] All treatments were generally well tolerated. Study 1 entailed 19/20 completers with one discontinuation from adverse events (AEs) (rhabdomyolysis (Grade 2) while receiving GS-7340 SA). All subjects completed Study 2, while 33 of 34 subjects completed Study 3. No Grade 3 or 4 AE was observed in the studies. In Study 1, when dosed as EVG/COBI/FTC/GS-7340, GS-7340 (25 mg) and resulting TFV exposures were substantially higher versus GS-7340 SA (GMR (90% CI) GS-7340 AUC_{last}: 222 (200, 246) and C_{max}: 223 (187, 265); TFV AUC_{tau}: 307 (290, 324), C_{max}: 368 (320, 423)). In Study 2, when dosed as GS-7340 plus COBI versus GS-7340 SA, GS-7340 exposures were similarly high, suggesting that the interaction observed in Study 1 was COBI-mediated (GMR (90% CI) GS-7340 AUC_{last}: 265 (229, 307) and C_{max}: 283 (220, 365, TFV AUC_{tau}: 331 (310, 353), C_{max}: 334 (302, 370), and C_{tau}: 335 (312, 359)). In Study 3, upon dose adjustment of GS-7340 to 10 mg, EVG/COBI/FTC/GS-7340 (150/150/200/10 mg) versus Reference resulted in comparable GS-7340 and TFV exposures. (GMR (90% CI) GS-7340 AUC_{last}: 89.0 (76.7, 103) and C_{max}: 97.3 (82.1, 115), TFV AUC_{last}: 124 (113, 136), C_{max}: 113 (98.8, 129), and C_{tau}: 120 (103, 140)).

EVG/COBI/FTC/GS-7340 STR provided similar EVG, COBI, and FTC exposures versus reference treatments and historical data.

[0358] GS-7340 and TFV exposures increase ~2-3 fold following coadministration with COBI or as EVG/COBI/FTC/GS-7340 dosing, which may be due to COBI inhibition of Pgp-mediated intestinal secretion of GS-7340. With a 10 mg dose of GS-7340, EVG/COBI/FTC/GS-7340 provided comparable GS-7340 and TFV exposures as GS-7340 at 25 mg and ~90% lower TFV exposure versus EVG/COBI/FTC/TDF.

Biological Example 6

[0359] EVG/COBI/FTC/TDF and EVG/COBI/FTC/tenofovir alafenamide hemifumarate were administered as single tablet regimens (STR) in a Phase 2 clinical trial evaluating safety and efficacy in HIV+ treatment-naïve adults. All subjects had HIV-1 RNA >5000 c/ml. Week 24 data indicated that treatment with the two STRs resulted in 87% of subjects on EVG/COBI/FTC/tenofovir alafenamide hemifumarate and 90% of subjects on EVG/COBI/FTC/TDF having HIV-1 RNA <50 c/ml. The EVG/COBI/FTC/tenofovir alafenamide hemifumarate STR was well tolerated, and relative to the known safety profile of EVG/COBI/FTC/TDF, no new or unexpected adverse drug reactions were identified.

[0360] Renal function was assessed in the subjects at week 24. When compared with subjects taking EVG/COBI/FTC/TDF, subjects taking EVG/COBI/FTC/ tenofovir alafenamide hemifumarate had significantly less reduction in the estimated glomerular filtration rate (eGFR), a trend towards less proteinuria, and statistically less tubular proteinuria. These differences may represent a reduction in subclinical tenofovir-associated nephrotoxicity.

[0361] To assess bone mineral density, dual-energy X-ray absorptiometry scans were performed at baseline and week 24. Subjects taking EVG/COBI/FTC/ tenofovir alafenamide hemifumarate experienced a significantly smaller reduction in bone mineral density at both spine and hip after 24 weeks, compared with subjects taking EVG/COBI/FTC/TDF. Importantly, the proportion of subjects with >3% decrease from baseline in hip bone mineral density was 10-fold lower in

the EVG/COBI/FTC/tenofovir alafenamide hemifumarate group than the EVG/COBI/FTC/TDF group (3.0% vs. 31.6%).

[0362] Together, these data support the hypothesis that TDF-associated renal and bone toxicity is driven by circulating tenofovir, as tenofovir levels are reduced by 90% in subjects administered EVG/COBI/FTC/tenofovir alafenamide hemifumarate.

[0363] All references, publications, patents, and patent documents cited herein are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

[0364] The use of the terms "a," "an," "the," and similar articles and the like in the context of describing the invention (including the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to"), unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein may be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention, unless otherwise claimed. No language in the specification should be construed as indicating any nonclaimed element as essential to the practice of the invention.

[0365] The embodiments within the specification provide an illustration of embodiments of the invention and should not be construed to limit the scope of the invention. The skilled artisan recognizes that many other embodiments are

encompassed by the claimed invention and that it is intended that the specification and examples be considered as exemplary only, with the true scope and spirit of the invention being indicated by the following claims.

WHAT IS CLAIMED IS:

1. A composition comprising: cobicistat, or a pharmaceutically acceptable salt thereof; and tenofovir alafenamide hemifumarate.

2. The composition of claim 1 comprising: 50-500 mg of cobicistat, or a pharmaceutically acceptable salt thereof; and 3-40 mg of tenofovir alafenamide hemifumarate.

3. The composition of claim 1 or 2, further comprising a pharmaceutically acceptable carrier or diluent.

4. A method of treating a viral infection in a human comprising administering a composition of any one of claims 1-3 to the human.

5. A method of treating a viral infection in a human comprising coadministering cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, to the human.

6. A method of inhibiting activity of a retroviral reverse transcriptase comprising coadministering cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate.

7. The method of claim 6, wherein the coadministering of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, is in a human.

8. Use of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, for the prophylactic or therapeutic treatment of a viral infection in a human.

9. Use of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, for the manufacture of a medicament for treating a viral infection in a human.

10. Use of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase.

11. The use of claim 10, wherein the medicament is for inhibiting activity of a retroviral reverse transcriptase in a human.

12. A method of boosting an anti-viral effect of tenofovir alafenamide hemifumarate in a human comprising administering a composition of any one of claims 1-3 to the human.

13. A method of boosting an anti-viral effect of tenofovir alafenamide hemifumarate in a human comprising coadministering cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate to the human.

14. The method of claim 13, wherein 50-500 mg of cobicistat, or a pharmaceutically acceptable salt thereof, is coadministered with 3-40 mg of tenofovir alafenamide hemifumarate.

15. A method of inhibiting Pgp-mediated intestinal secretion of tenofovir alafenamide hemifumarate in a human comprising administering a composition of any one of claims 1-3 to the human.

16. A method of inhibiting Pgp-mediated intestinal secretion of tenofovir alafenamide hemifumarate in a human by coadministration of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate.

17. The method of claim 16, wherein 50-500 mg of cobicistat, or a pharmaceutically acceptable salt thereof, is coadministered with 3-40 mg of tenofovir alafenamide hemifumarate.

18. The method of claim 4 or 5, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

19. The use of claim 8 or 9, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

20. The method of any one of claims 12-14, wherein the virus is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

21. A composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir.

22. A composition comprising: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir.

23. A method of treating a viral infection in a human comprising administering a composition of claim 21 or 22 to the human.

24. A method of treating a viral infection in a human comprising coadministering (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir to the human.

25. The method of claim 24 comprising coadministering (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir to the human.

26. The use of the composition of claim 21 or 22 for the prophylactic or therapeutic treatment of a viral infection in a human.

27. Use of (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir for the manufacture of a medicament for treating a viral infection in a human.

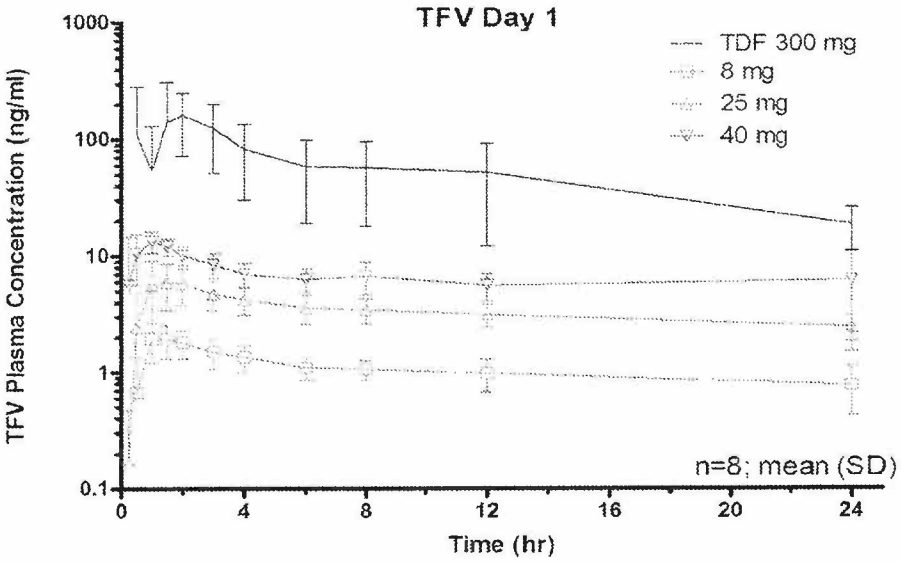
28. Use of (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof: (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir for the manufacture of a medicament for treating a viral infection in a human.

29. A composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

30. A composition comprising: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

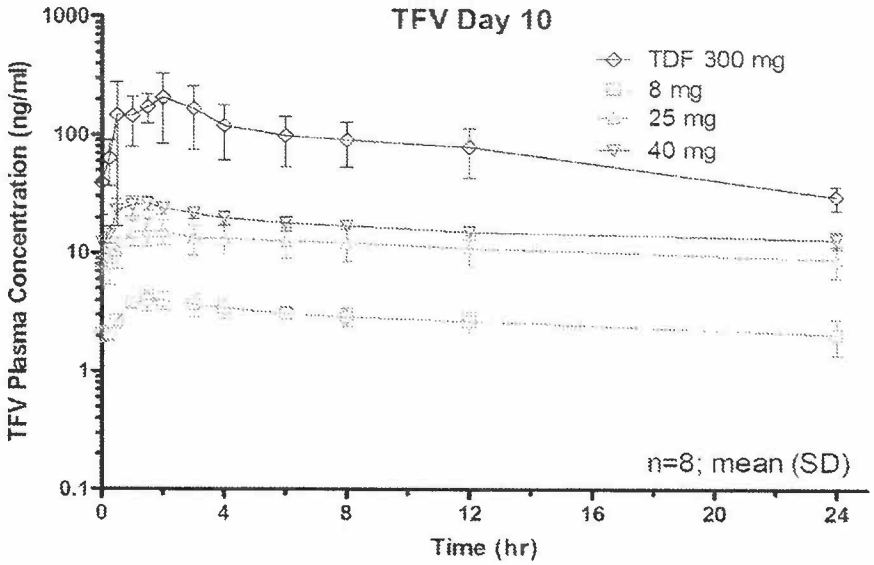
31. The method of any one of claims 23-25, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

32. The use of any one of claims 26-28, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).



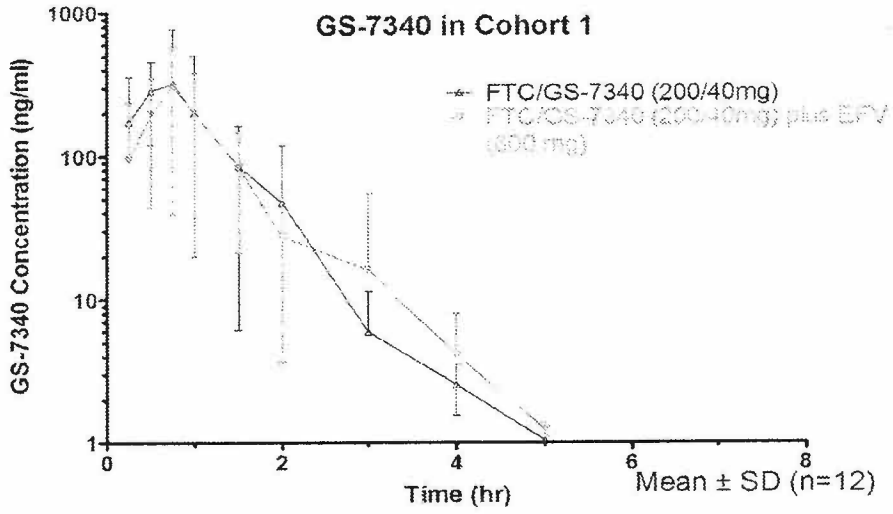
Day 1 PK Mean (%CV)	GS-7340 8 mg	GS-7340 25 mg	GS-7340 40 mg	TDF 300 mg
Cmax (ng/ml)	2 (30)	6.5 (40)	15 (36)	210 (52)
AUClast (ng.hr/ml)	25 (27)	70 (37)	143 (40)	1132 (48)

Figure 1



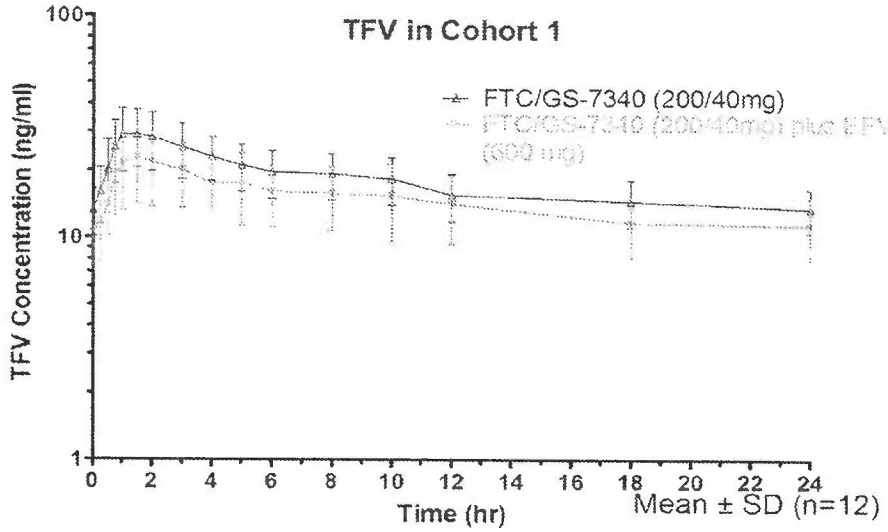
Day 10 PK Mean (%CV)	GS-7340 8 mg	GS-7340 25 mg	GS-7340 40 mg	TDF 300 mg
Cmax (ng/ml)	3.9 (28)	16 (22)	28 (9)	260 (43)
AUCtau (ng.hr/ml)	66 (19)	268 (29)	389 (11)	2090 (44)

Figure 2



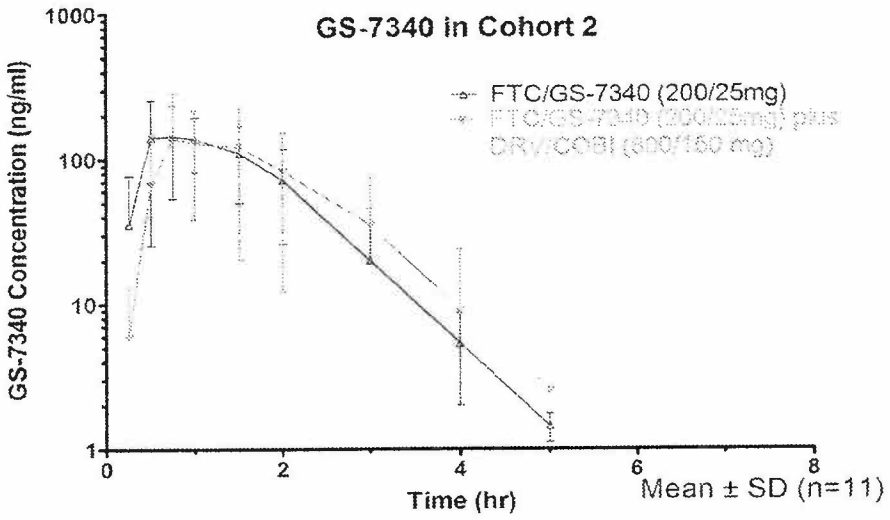
	GS-7340 PK in Cohort 1	
Mean (%CV)	FTC/GS-7340 (200/40 mg)	FTC/GS-7340 plus EFV 600 mg
AUC_{last} (ng.hr/ml)	330.5 (63)	285.5 (47)
C_{max} (ng/ml)	481.3 (83)	390.8 (62)

Figure 3A



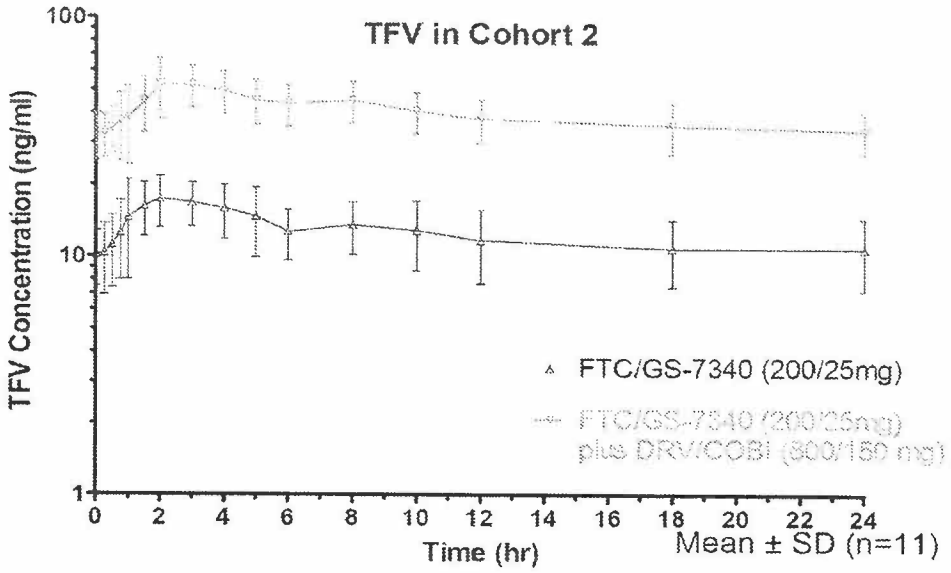
	TFV PK in Cohort 1	
Mean (%CV)	FTC/GS-7340 (200/40 mg)	FTC/GS-7340 plus EFV 600 mg
AUC_{0-24} (ng.hr/ml)	427.5 (23)	350.2 (32)
C_{max} (ng/ml)	31.4 (25)	24.0 (35)
C_{tau} (ng/ml)	13.5 (22)	11.3 (32)

Figure 3B



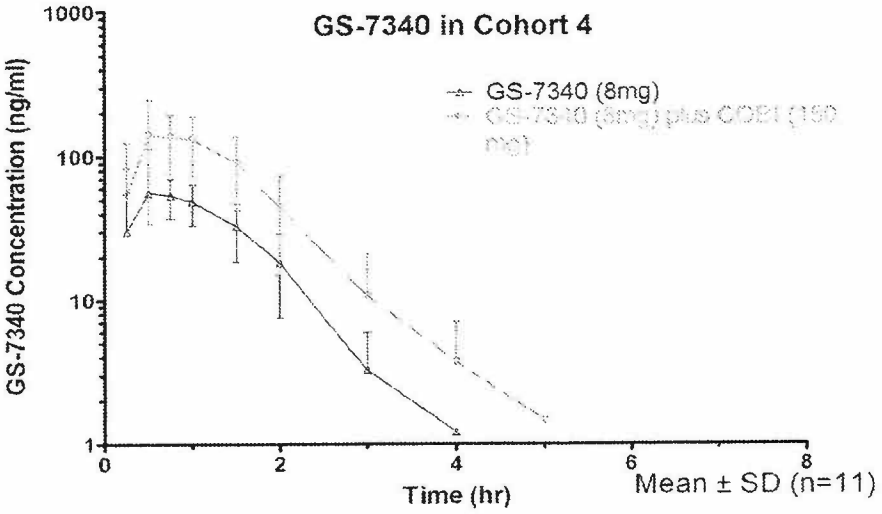
GS-7340 PK	Cohort 2		Cohort 3
Mean (%CV)	FTC/GS-7340 (200/25 mg)	FTC/GS-7340 plus DRV/COBI (800/150 mg)	FTC/GS-7340 (200/25 mg) plus DRV/COBI (800/150 mg)
AUC_{last} (ng.hr/ml)	245.6 (42)	243.9 (41)	271.0 (39)
C_{max} (ng/ml)	208.3 (40)	215.0 (59)	287.4 (73)

Figure 4A



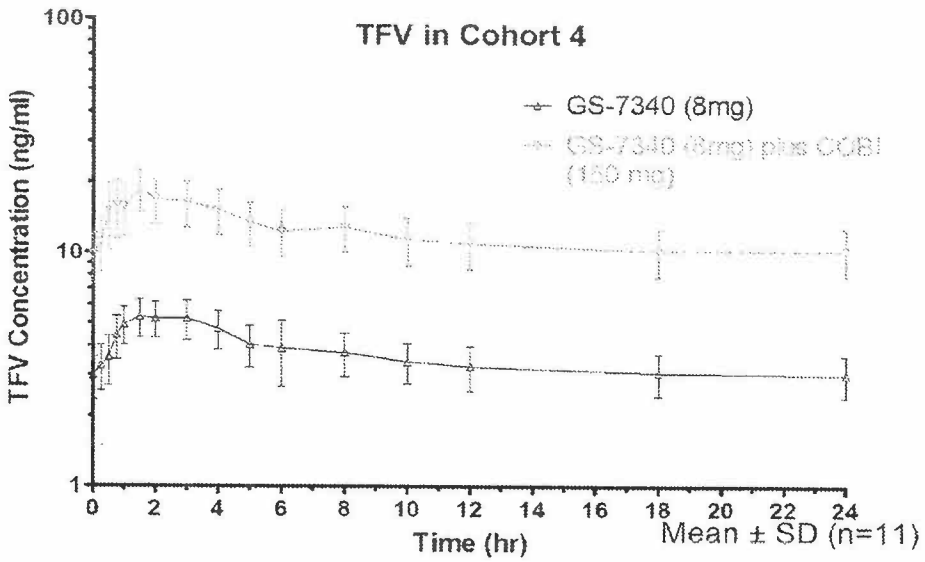
TFV PK	Cohort 2		Cohort 3
Mean (%CV)	FTC/GS-7340 (200/25 mg)	FTC/GS-7340 plus DRV/COBI (800/150 mg)	FTC/GS-7340 (200/25 mg) plus DRV/COBI (800/150 mg)
AUC_{tau} (ng.hr/ml)	299.2 (29)	953.4 (20)	967.6 (13)
C_{max} (ng/ml)	18.3 (28)	57.4 (23.2)	57.7 (15)
C_{tau} (ng/ml)	10.8 (33)	33.7 (20)	36.2 (13)

Figure 4B



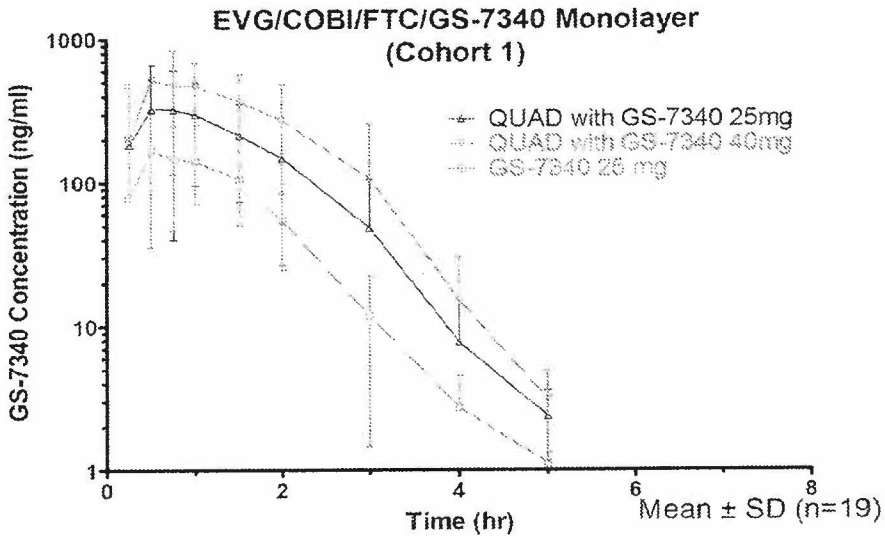
	Cohort 4			
	Steady State PK		Single Dose PK	
Mean (%CV)	GS-7340 (8 mg)	GS-7340 (8 mg) plus COBI (150 mg)	GS-7340 (8 mg)	GS-7340 (8 mg) plus COBI (150 mg)
AUC_{last} (ng.hr/ml)	81.2 (44)	213.3 (38)	64.7 (34)	188.0 (27)
C_{max} (ng/ml)	71.0 (73)	189.9 (46)	49.9 (38)	141.5 (33)

Figure 5A



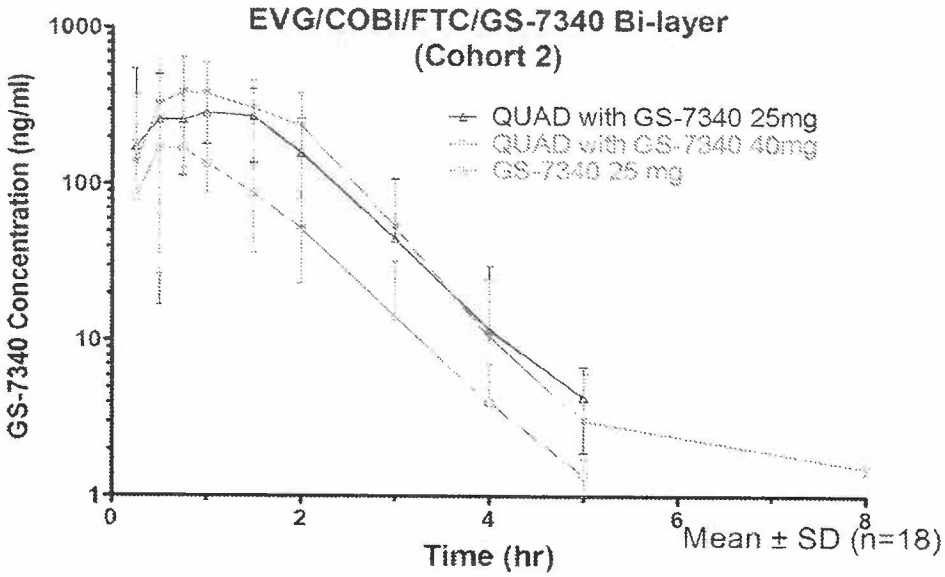
	TFV PK Multiple Dose PK	
Mean (%CV)	GS-7340 (8 mg)	GS-7340 (8 mg) plus COBI (150 mg)
AUC_{tau} (ng.hr/ml)	86.1 (19)	286.9 (22)
C_{max} (ng/ml)	5.8 (19)	19.3 (20)
C_{tau} (ng/ml)	3.0 (20)	10.2 (24)

Figure 5B



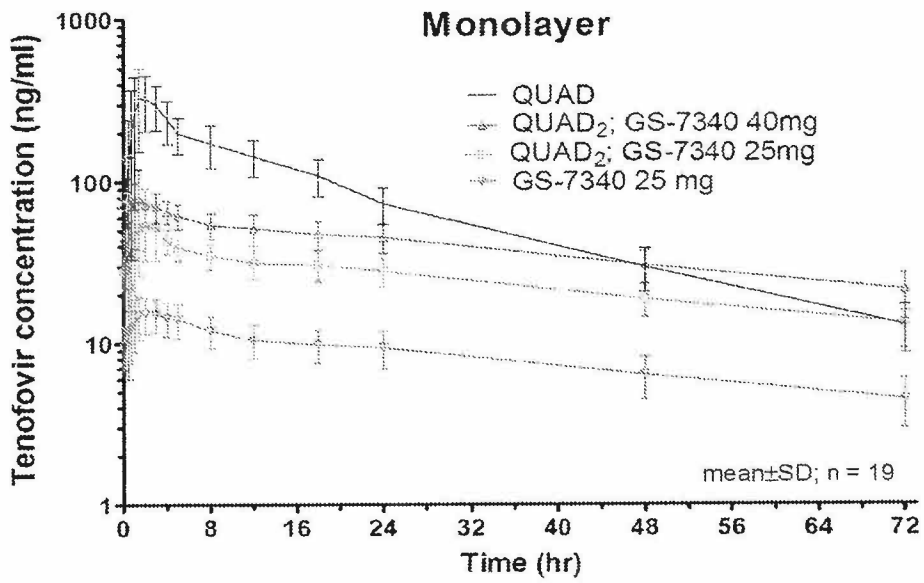
Monolayer Mean (%CV)	$QUAD_2$ with GS-7340 25 mg	$QUAD_2$ with GS-7340 40 mg	GS-7340 25 mg
C_{max} (ng/ml)	506 (54)	793 (52)	215 (55)
AUC_{tau} (ng.hr/ml)	552 (41)	929 (34)	243 (42)

Figure 6



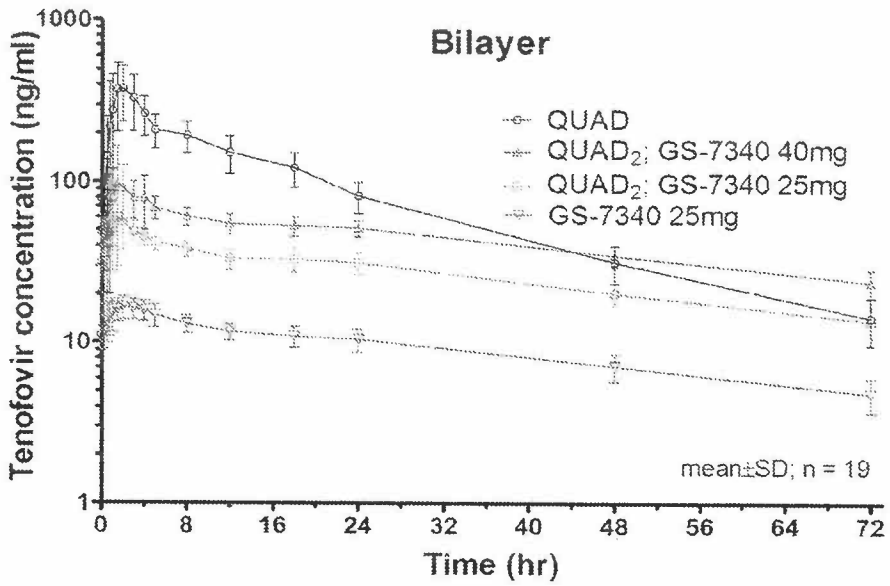
Bi-layer Mean (%CV)	$QUAD_2$ with GS-7340 25 mg	$QUAD_2$ with GS-7340 40 mg	GS-7340 25 mg
C_{max} (ng/ml)	472 (58)	587 (33)	211 (44)
AUC_{tau} (ng.hr/ml)	559 (29)	760 (27)	245 (34)

Figure 7



Monolayer Mean (%CV)	$QUAD_2$ 25 mg	$QUAD_2$ 40 mg	GS-7340 25 mg	QUAD
C_{max} (ng/ml)	66 (51)	103 (64)	16 (25)	445 (29)
C_{tau} (ng/ml)	28.1 (20)	45.4 (21)	9.40 (26)	73.1 (25)
AUC_{tau} (ng.hr/ml)	837 (18)	1310 (21)	274 (24)	3760 (22)

Figure 8



Bi-layer Mean (%CV)	$QUAD_2$ 25 mg	$QUAD_2$ 40 mg	GS-7340 25 mg	QUAD
C_{max} (ng/ml)	71.9 (57)	117 (60)	17.5 (15)	505 (27)
C_{tau} (ng/ml)	31.3 (15)	51.4 (12)	10.5 (17)	81.6 (22)
AUC_{tau} (ng.hr/ml)	899 (13)	1460 (16)	301 (13)	4120 (22)

Figure 9

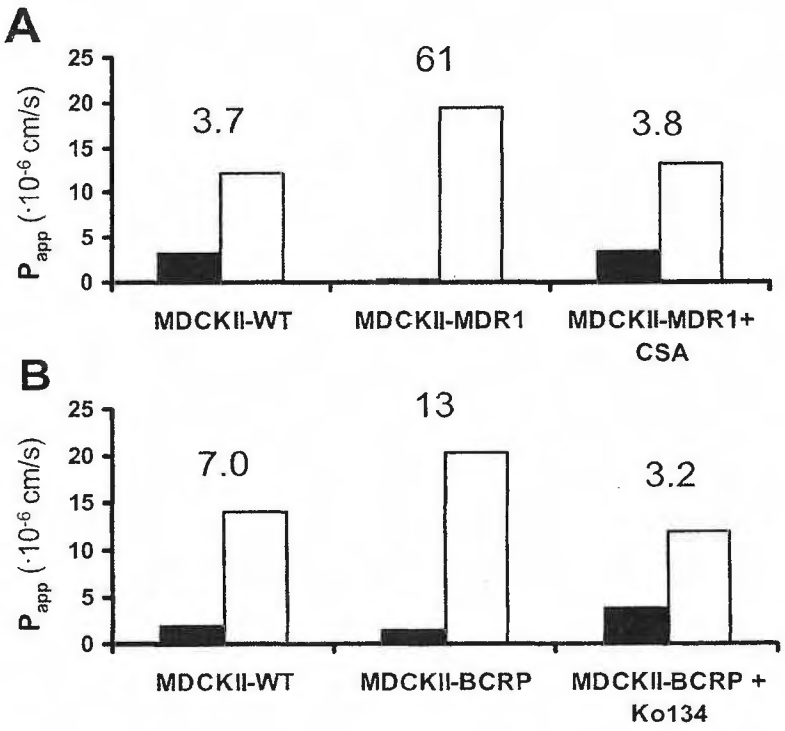

A
61
3.7
3.8
25
20
15
10
5
0
P_{app} ($\cdot 10^{-6}$ cm/s)
MDCKII-WT
MDCKII-MDR1
MDCKII-MDR1+ CSA
B
13
7.0
3.2
25
20
15
10
5
0
P_{app} ($\cdot 10^{-6}$ cm/s)
MDCKII-WT
MDCKII-BCRP
MDCKII-BCRP + Ko134

Figure 10

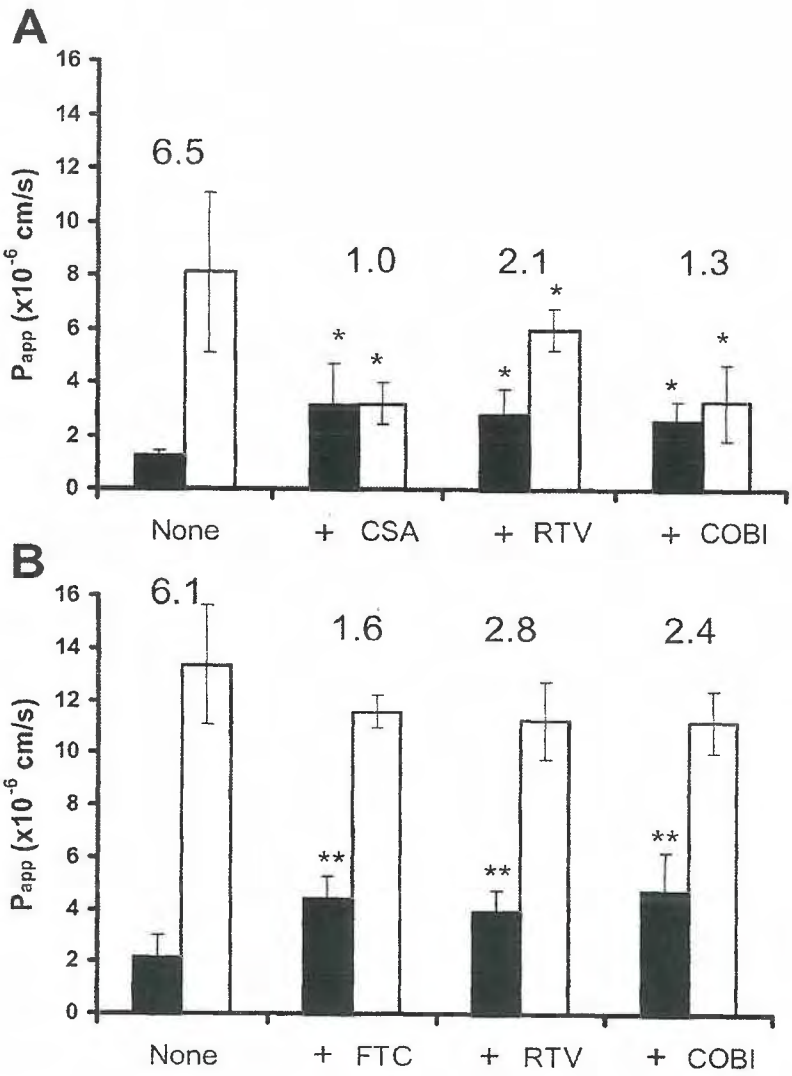

A
16
14
12
10
8
6
4
2
0
P_{app} ($x10^{-6}$ cm/s)
6.5
1.0
2.1
1.3
*
None
+ CSA
+ RTV
+ COBI
B
6.1
1.6
2.8
2.4
**
None
+ FTC
+ RTV
+ COBI

Figure 11

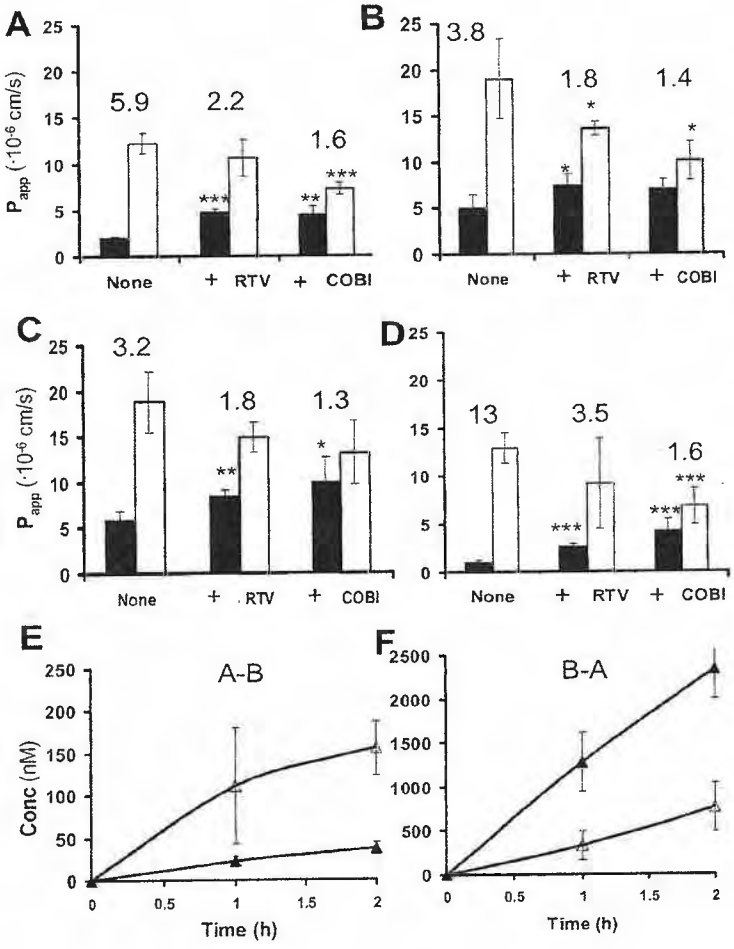

A
B
C
D
E
F
P_{app} ($\cdot 10^{-6}$ cm/s)
5.9
2.2
1.6
3.8
1.8
1.4
3.2
1.8
1.3
13
3.5
1.6
None
+ RTV
+ COBI
A-B
B-A
Conc (nM)
Time (h)

Figure 12

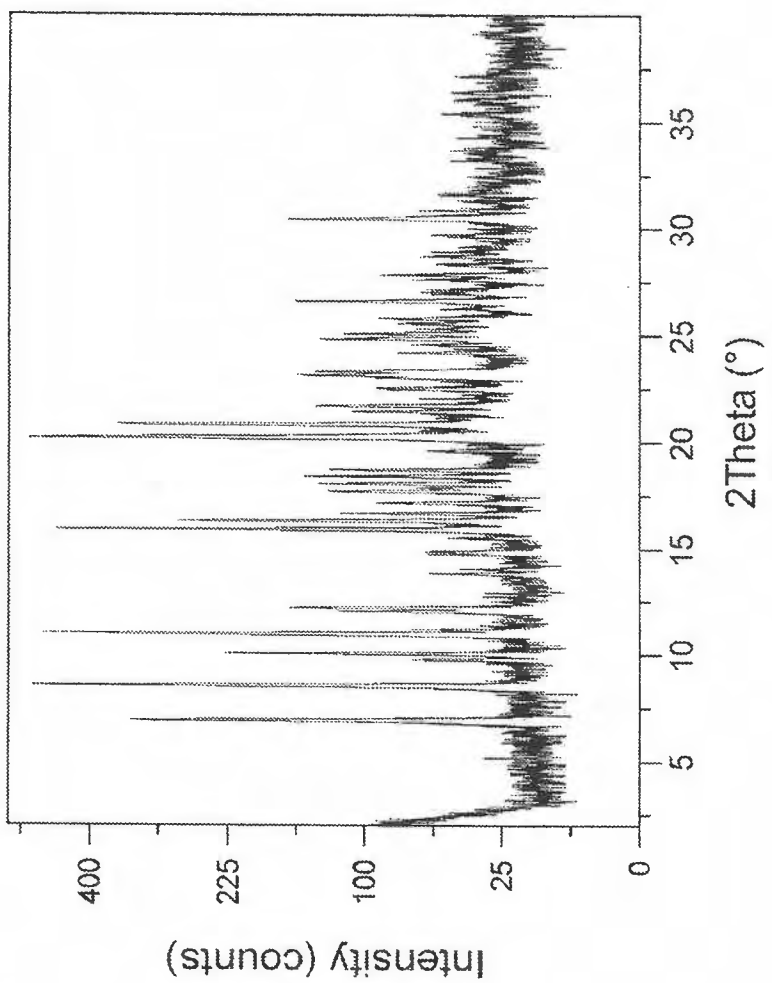


Figure 13

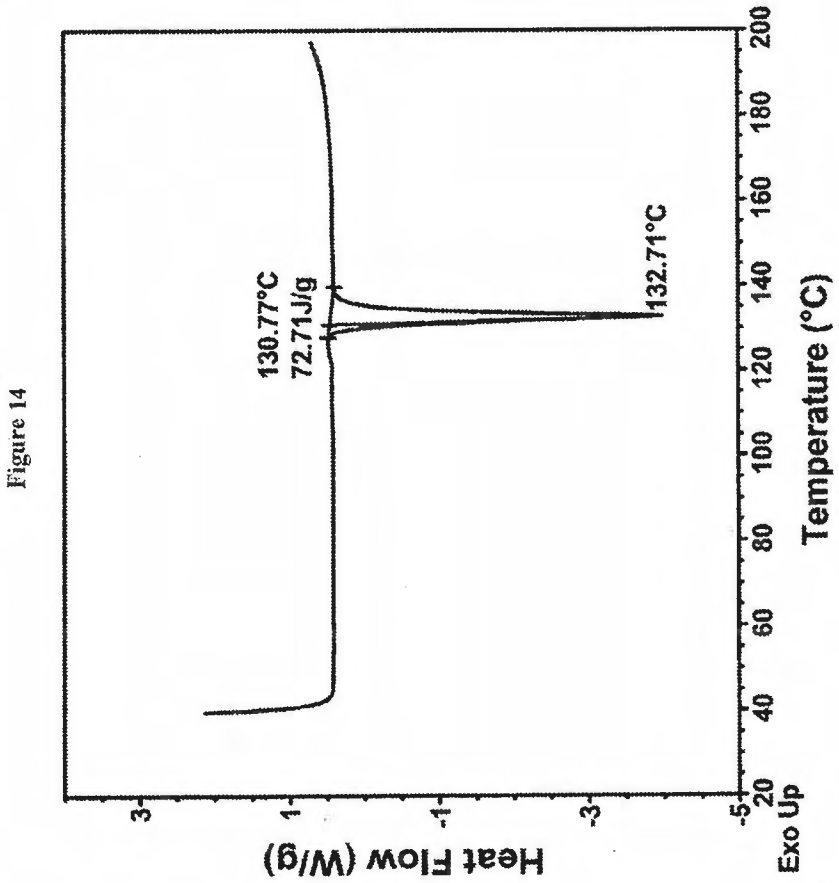

130.77°C
72.71J/g
132.71°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
3
1
-1
-3
-5
20
40
60
80
100
120
140
160
180
200

Figure 14

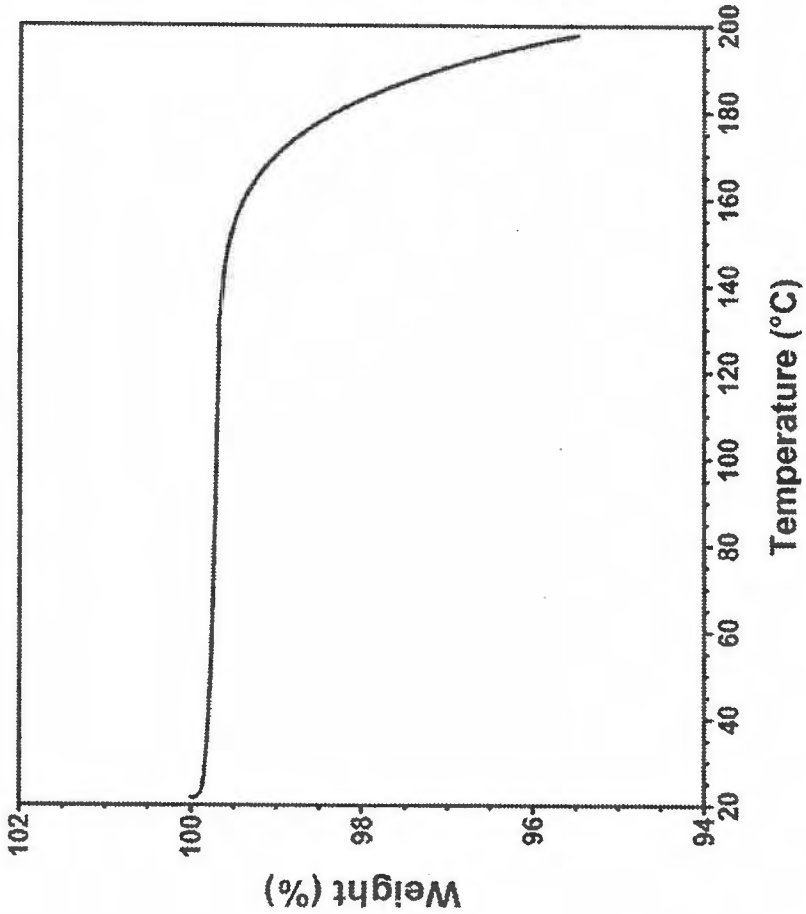

Weight (%)
102
100
98
96
94
Temperature (°C)
20
40
60
80
100
120
140
160
180
200

Figure 15

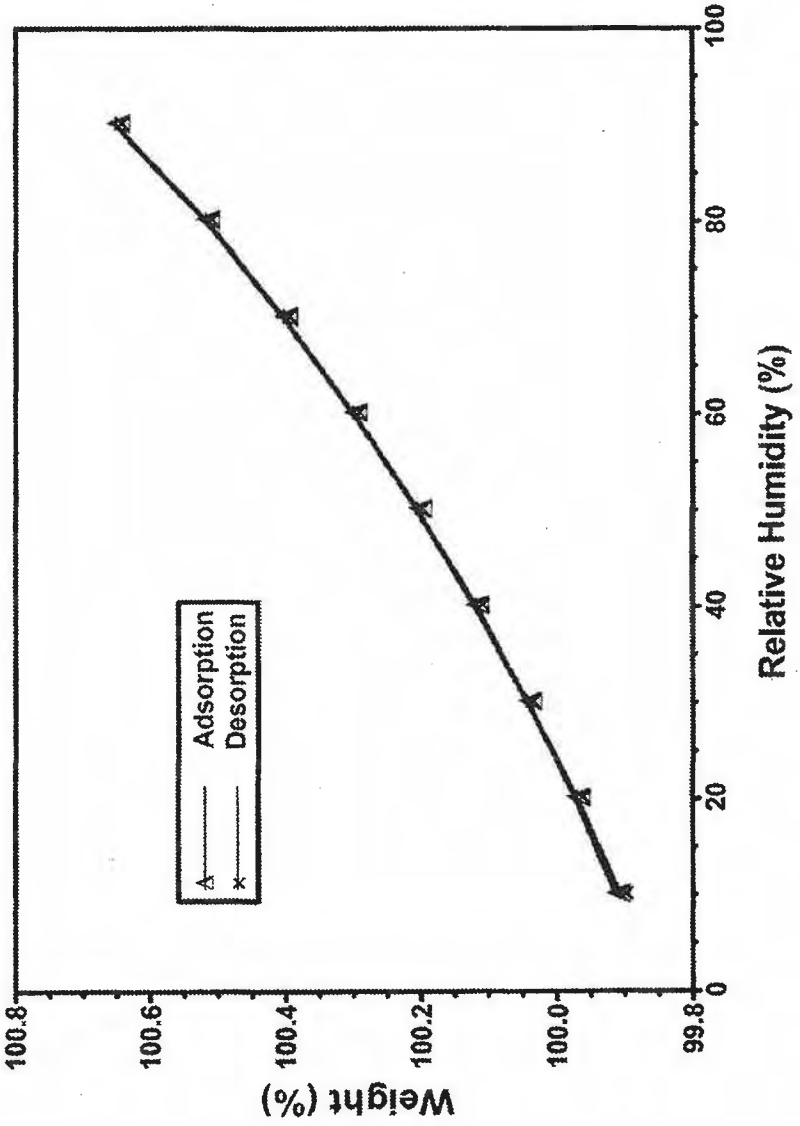

Weight (%)
100.8
100.6
100.4
100.2
100.0
99.8
Relative Humidity (%)
0
20
40
60
80
100
Adsorption
Desorption

Figure 16

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/024438

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/513 A61K31/5377 A61K31/675 A61K31/47 A61P31/12
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	"GS-7340", Thomson Reuters Drug News, 2002, XP002694095, Retrieved from the Internet: URL:http://integrity.thomson-pharma.com/integrity/xmlxsl/pk_ref_list.xml_show_llista t_refs?p_session_id=2207762&p_orig=&p_count=45&p_ [retrieved on 2013-01-29] the whole document ----- -/--	1-32

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2013	16/04/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Renard, Delphine

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/024438

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	"Phase II trial investigates GS-7340 as part of a new treatment regimen", Thomson Reuters Drug News, 26 January 2012 (2012-01-26), XP055051645, Retrieved from the Internet: URL:http://integrity.thomson-pharma.com/integrity/xmlxsl/pk_ref_list.xml_related_ref_to?p_id=315936&p_origen=PRO&p_tsearch=#link [retrieved on 2013-01-29] "phase IIa studies ....10 times lower than than that of Viread" "once daily tablet containing GS-7340 (10 mg), cobicistat (150 mg), elvitegravir (150 mg) and emtricitabine (200 mg)"	1-32
A	WO 2010/091197 A2 (GILEAD SCIENCES INC [US]; OLIYAI REZA [US]; MENNING MARK M [US]; KOZIA) 12 August 2010 (2010-08-12) claims 1, 6; examples 1-4	1-12
A	RICHARD ELION ET AL: "Phase 2 study of cobicistat versus ritonavir each with once-daily atazanavir and fixed-dose emtricitabine/tenofovir df in the initial treatment of HIV infection", AIDS, vol. 25, no. 15, 1 September 2011 (2011-09-01), pages 1881-1886, XP055051636, ISSN: 0269-9370, DOI: 10.1097/QAD.0b013e32834b4d48 abstract the whole document	1-12
X,P	Liz Highleyman: "ICAAC 2012: New Tenofovir Pro-drug Matches Potency of Original Version but with Less Toxicity", hivandhepatitis.com, 6 December 2012 (2012-12-06), XP055052016, Retrieved from the Internet: URL:http://www.hivandhepatitis.com/hiv-aids/hiv-aids-topics/hiv-treatment/3853-new-tenofovir-pro-drug-matches-potency-of-original-version-but-with-less-toxicity [retrieved on 2013-02-01] the whole document	1-32

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/024438

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	LEPIST EI ET AL: "Cobicistat Boosts the Intestinal Absorption of Transport Substrates, Including HIV Protease Inhibitors and GS-7340, In Vitro", ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, DC, US, vol. 56, no. 10, 1 October 2012 (2012-10-01), pages 5409-5413, XP009166632, ISSN: 0066-4804 the whole document	1-32
E	WO 2013/025788 A1 (GILEAD SCIENCES INC [US]; LIU DAZHAN [CA]; SHI BING [US]; WANG FANG [U) 21 February 2013 (2013-02-21) claims 1,14,17; tables 2-3	1-32

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/024438

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010091197 A2	12-08-2010	AR 075369 A1	30-03-2011
		AU 2010210598 A1	25-08-2011
		CA 2750521 A1	12-08-2010
		CN 102307573 A	04-01-2012
		EA 201190125 A1	30-01-2012
		EC SP11011307 A	31-10-2011
		EP 2393485 A2	14-12-2011
		JP 2012517432 A	02-08-2012
		KR 20110122729 A	10-11-2011
		PE 09942011 A1	24-01-2012
		SG 173544 A1	29-09-2011
		TW 201040142 A	16-11-2010
		US 2010285122 A1	11-11-2010
		UY 32424 A	30-09-2010
		WO 2010091197 A2	12-08-2010
WO 2013025788 A1	21-02-2013	US 2013065856 A1	14-03-2013
		WO 2013025788 A1	21-02-2013

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(54) Title: MEDICAMENT COMPRISING A PHARMACEUTICAL COMBINATION OF DOLUTEGRAVIR, EMTRICITABINE AND TENOFOVIR

(57) Abstract: The present invention concerns a pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir or a prodrug thereof, wherein preferably the compounds are present in a specific weight ratio and/or in specific amounts, for use as a medicament, preferably in treatment of viral infection/disease such as an HIV infection. Further, the present invention relates to a pharmaceutical composition comprising the pharmaceutical combination and optionally further pharmaceutical excipient(s)

MEDICAMENT COMPRISING A PHARMACEUTICAL COMBINATION OF DOLUTEGRAVIR, EMTRICITABINE AND TENOFOVIR

The present invention concerns a pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir or a prodrug thereof, wherein preferably the compounds are present in a specific weight ratio and/or in specific amounts, for use as a medicament, preferably in treatment of viral infection/disease such as an HIV infection. Further, the present invention relates to a pharmaceutical composition comprising the pharmaceutical combination and optionally further pharmaceutical excipient(s).

Background

A virus infection can be regarded as infiltration of a living organism, such as a human being, by a virus. After having been infiltrated, the organism might respond to said infiltration. For example, in humans the white blood cells of the immune system help to protect the body from viruses by destroying the cells infected by the virus. However, the destruction of the infected cells may lead to a release of intact viral particles, which can infect further so far non-infected cells and result in specific diseases or disorders of the organism.

An infiltration by the human immunodeficiency virus (HIV) may cause acquired immunodeficiency syndrome (AIDS). In that case the immune system of an organism, such as a human being, is weakened such that said system is not able to antagonize further life-threatening opportunistic infections. At present an HIV infection is said to be not curable, such that it is a main target to prevent or at least significantly slow down the proliferation of the corresponding virus. Since the treatment of an HIV infection is quite complex, combination therapies have been proposed. Combination therapies are therapies in which two or more pharmaceutical active agents are used. For example, in clinical trials a combination called "572-Trii" comprising 50 mg dolutegravir, 300 mg lamivudine and 600 mg abacavir seems to be very promising.

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However, recently concerns against combination therapies have been reported. Firstly, the interaction between two or more drugs may affect the intended therapeutic activity of each drug and secondly, the interaction may increase the levels of toxic metabolites (Guidance for Industry, 1999). The interaction may also heighten or lessen the side effects of each drug. Hence, upon administration of two or more drugs to treat a disease it is unpredictable what change will occur in the negative side effects of each drug. Additionally, it is difficult to accurately predict when the effects of the interaction between the two or more drugs will become manifest. For example, metabolic interactions between drugs may become apparent upon initial administration of the second drug, after the two have reached a steady state concentration or upon discontinuation of one of the drugs (Guidance for Industry, 1999).

Raffi Francois et al, Lancet (North American edition), vol. 381, no. 9868, March 2013, pages 735-743, describes a study wherein the HIV integrase inhibitors, dolutegravir and raltegravir are compared. In particular either 50 mg of dolutegravir or 400 mg of raltegravir in combination with two known NRTI-backbones (coformulated tenofovir/emtricitabine or abacavir/lamivudine), respectively, are administered to patients with HIV-1 infection. As a result of the study it turned out that dolutegravir can be regarded as suitable alternative to raltegravir.

However, the combinations suggested in Raffi still seem to be improvable in view of their efficiency and/or safety. In particular, the reduction of possible side effects, e.g. when administered to older people or to people having an impaired immune system, is desirable.

Thus, it was an object of the present invention to overcome the above-illustrated drawbacks. In particular, it was an object of the invention to provide an improved medicament or treatment regime for the treatment of viral diseases, in particular HIV. Preferably, it was an object of the present invention to provide a medicament which leads to advantageous therapeutic effects when treating viral diseases, in

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particular HIV. Further, undesirable side effects should be prevented or at least significantly reduced.

Further, it was an object to provide a medicament wherein the total amount of pharmaceutical active agent(s) is suitable for preparing a dosage form having a comfortable size such that patient compliance can be improved.

The objects of the present invention have been unexpectedly solved by a combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir, having a specific weight ratio of (a) dolutegravir to emtricitabine (b) and preferably being administered in specific amounts.

Summary of the Invention

This invention provides a pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament.

This invention also provides a pharmaceutical composition comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1 : 1 to 1 : 3.

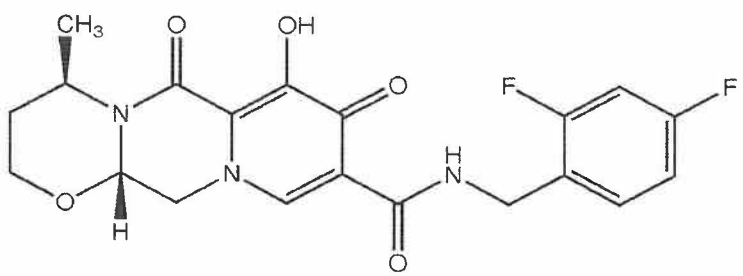
This invention in addition provides a method of treating a subject afflicted with a viral infection, preferably afflicted with an HIV infection, comprising periodically administering to the subject an amount of (a) dolutegravir, (b) emtricitabine and (c) tenofovir, wherein the amounts when taken together are effective to treat the subject, wherein preferably the subject is a human.

Detailed Description of the Invention

The pharmaceutical combination of the present invention comprises (a) dolutegravir as a first active pharmaceutical ingredient.

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The chemical name of (a) dolutegravir, also known as S/GSK1349572 or just "572", is (4R,12aS)-N-(2,4-difluorobenzyl)-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexa-hydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide. Dolutegravir is reported to have anti-viral activity, since it is considered to be an integrase inhibitor. Integrase is a viral enzyme for integrating (retro)viral DNA into the genome of the host cell and the inhibition of the integrase has a massive influence on the replication of the retrovirus. By inhibiting said integrase the replication of the retrovirus can be significantly reduced or even prevented. Thus, dolutegravir is assumed to be useful for the treatment of infections/diseases caused by viruses such as hepatitis B and HIV. In particular dolutegravir is assumed to be useful for the treatment of HIV infections and/or AIDS. 4R,12aS)-N-(2,4-difluorobenzyl)-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexa-hydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide (dolutegravir) is represented by the following chemical structure:



Formula (I)

In this regard it is noted that in the present invention the term dolutegravir comprises 4R,12aS)-N-(2,4-difluorobenzyl)-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide according to Formula (I). In addition, the term "dolutegravir" comprises all the pharmaceutically acceptable salts, hydrates and/or solvates thereof. Dolutegravir can be obtained according to the procedures as for example outlined in WO 2006/116764 or WO 2010/068253.

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Acids, which are used to prepare pharmaceutically acceptable acid addition salts, are preferably those which form non-toxic acid addition salts. Examples of the acid addition salts are mineral acid salts such as hydrochloride, hydrobromide, hydroiodide, hemisulfate, sulfate, nitrate, dihydrogenphosphate, hydrogen phosphate, hydrogen carbonate, carbonate or perchlorate salts; organic acid salts such as formate, acetate, propionate, lactates, maleates, fumarates, tartrates, malates, citrates, ascorbates; acidic amino acid salts such as aspartates or glutamates and methanesulfonates, benzenesulfonates, or p-toluenesulfonates.

Examples of suitable basic salts include alkali metal salts such as sodium or potassium salts; earth-alkali metal salts such as calcium or magnesium salts; ammonium salts; aliphatic amine salts such as trimethylamine, triethylamine, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine or procaine salts; aralkyl amine salts such as N,N-dibenzylethylonediamine salts; heterocyclic aromatic amine salts such as pyridine salts, methyl pyridine salts, quinoline salts or isoquinoline salts; quaternary ammonium salts such as tetramethylammonium salts, tetraethylammonium salts, benzyltrimethylammonium salts, benzyltriethyl-ammonium salts, benzyltributylammonium salts, methyltrioctylammonium salts or tetrabutylammonium salts; and basic amino acid salts such as arginine salts or lysine salts.

Preferably, dolutegravir is in the form of a pharmaceutically acceptable salt. More preferred, dolutegravir is in the form of an alkali metal salt such as sodium or potassium salt or in the form of an earth-alkali metal salt such as calcium or magnesium salt. More preferred, dolutegravir is in the form of a sodium salt or a magnesium salt. Particularly preferred, dolutegravir is used in form of the sodium salt, especially the mono-sodium salt.

It is alternatively particularly preferred that dolutegravir is used in its free form (not as salt).

The sodium salt of dolutegravir and a specific crystalline form of this sodium salt or a hydrate thereof are disclosed in WO 2010/068253. Amorphous dolutegravir sodium is described in WO 2013/038407.

Further, it is preferred that dolutegravir is present in a non-solvated/non-hydrated form.

In a preferred embodiment of the present invention all numbers referring to the weight (mg) or weight-% of dolutegravir are based on the weight of dolutegravir in its free form.

In the combination of the present invention, dolutegravir as the active ingredient can be provided in amorphous form, in crystalline form or as a mixture of both forms. Preferably, dolutegravir is present in crystalline form.

It is reported that its primary route of metabolism is glucuronidation. Dolutegravir is considered to be a substrate of CYP3A4, but only to a minor extent of about 15%. Further, dolutegravir demonstrates induction or inhibition of cytochrome P450 (CYP) isozymes in vitro.

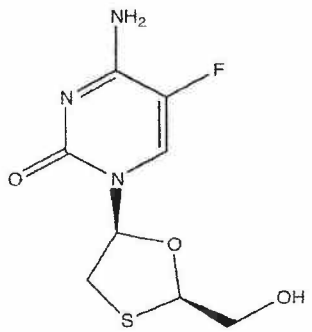
The pharmaceutical combination of the present invention comprises (b) emtricitabine as a second active pharmaceutical ingredient.

The chemical name of (b) emtricitabine is 5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3 oxathiolan-5-yl]cytosine. Emtricitabine is reported to be a substance with anti-viral activity since it is considered to be a nucleoside reverse transcriptase inhibitor. Reverse transcriptase is a viral DNA polymerase that is required for replication of the virus. The reverse transcriptase allows copying the single stranded RNA genome into a double stranded viral DNA, which is subsequently incorporated into the DNA of the host cell. Having been integrated in the host cell genome, viral particles are produced which in turn can infect so far uninfected host cells.

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Nucleoside analog reverse-transcriptase inhibitors (also known as NARTIs or NRTIs) are considered to inhibit/prevent the activity of reverse transcriptase by blocking its enzymatic function.

By inhibiting said reverse transcriptase the replication of the retrovirus can be significantly reduced or even prevented. Thus, emtricitabine is assumed to be useful for the treatment of infections/diseases caused by viruses such as hepatitis B and HIV. In particular emtricitabine is assumed to be useful for the treatment of HIV infections and/or AIDS. Emtricitabine is also known as 5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3 oxathiolan-5-yl]cytosine and is represented by the following chemical structure:



Formula (II)

In this regard it is noted that in the present invention the term "emtricitabine" comprises 5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3 oxathiolan-5-yl]cytosine according to Formula (II). In addition, the term "emtricitabine" comprises all the pharmaceutically acceptable salts, hydrates and/or solvates thereof. Emtricitabine can for example be obtained according to the procedures as outlined in EP 0 513 200 B2.

Emtricitabine possesses two chiral centers. Preferably emtricitabine is in the form of the cis-(-)-enantiomer.

Acids which are used to prepare pharmaceutically acceptable acid addition salts are preferably those which form non-toxic acid addition salts. Examples of the acid addition salts are mineral acid salts such as hydrochloride, hydrobromide, hydroiodide, hemisulfate, sulfate, nitrate, dihydrogen phosphate, hydrogen phosphate, hydrogen carbonate, carbonate or perchlorate salts; organic acid salts such as formate, acetate, propionate, lactates, maleates, fumarates, tartrates, malates, citrates, ascorbates; acidic amino acid salts such as aspartates or glutamates and methanesulfonates, benzenesulfonates, or p-toluenesulfonates.

In a preferred embodiment emtricitabine is present in the form of its free base, i.e. not in the form of an acid addition salt.

Further, it is preferred that emtricitabine is present in a non-solvated/non-hydrated form.

In a preferred embodiment of the present invention all numbers referring to the weight (mg) or weight-% of emtricitabine are based on the weight of emtricitabine in its free form.

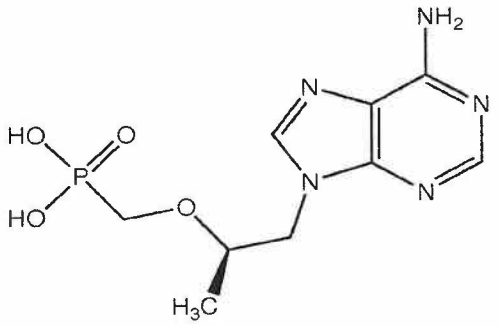
In the combination of the present invention, emtricitabine as the active ingredient can be provided in amorphous form, in crystalline form or as a mixture of both forms. Preferably, emtricitabine is present in crystalline form. Different polymorphic forms of crystalline emtricitabine are known. Preferably crystalline emtricitabine is polymorph form I.

It is reported that there is limited metabolism. The biotransformation of emtricitabine includes oxidation of the thioether-containing moiety to form sulphoxidediatereomers and conjugation with glucuronic acid to form 2'-O-glucuronide. Emtricitabine does not inhibit in vitro drug metabolism mediated by the following human CYP 450 isoenzymes: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4. Further, emtricitabine does not inhibit uridine-5-5'-diphosphoglucuronyl transferase, the enzyme responsible for glucuronidation.

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The pharmaceutical combination of the present invention comprises (c) tenofovir as a third active pharmaceutical ingredient.

The chemical name of (c) tenofovir is (*R*)-(1-(6-amino-9*H*-purin-9-yl)propan-2yloxy)methyl phosphonic acid. Like the above compounds (a) dolutegravir and (b) emtricitabine, compound (c) tenofovir is reported to be a substance with anti-viral activity. Tenofovir is considered to be a nucleotide reverse transcriptase inhibitor (NtRTI). NtRTIs, such as tenofovir, allegedly have a mode of action being quite similar to the ones of the nucleoside reverse transcriptase inhibitors (NRTI), such as emtricitabine mentioned above. Substantially, NtRTIs should disrupt the construction of a new piece of proviral DNA and thus reduce/prevent the replication of the (retro)virus. Consequently, tenofovir is assumed to be useful for the treatment of infections/diseases caused by viruses such as hepatitis B, HIV and/or AIDS, in particular HIV and/or AIDS. (*R*)-(1-(6-amino-9*H*-purin-9-yl)propan-2yloxy)methyl phosphonic acid (tenofovir) is represented by the following chemical structure:



Formula (III)

In this regard it is noted that in the present invention the term "tenofovir" comprises (*R*)-(1-(6-amino-9*H*-purin-9-yl)propan-2yloxy)methyl phosphonic acid according to Formula (III). In addition the term "tenofovir" comprises all the pharmaceutically acceptable salts, hydrates and/or solvates thereof. Tenofovir is inter alia described in WO 94/03467.

Acids which are used to prepare pharmaceutically acceptable acid addition salts are preferably those which form non-toxic acid addition salts. Examples of the acid addition salts are mineral acid salts such as hydrochloride, hydrobromide, hydroiodide, hemisulfate, sulfate, nitrate, dihydrogen phosphate, hydrogen phosphate, hydrogen carbonate, carbonate or perchlorate salts; organic acid salts such as formate, acetate, propionate, lactates, maleates, fumarates, tartrates, malates, citrates, ascorbates; acidic amino acid salts such as aspartates or glutamates and methanesulfonates, benzenesulfonates, or p-toluenesulfonates.

Examples of suitable basic salts include alkali metal salts such as sodium or potassium salts; earth-alkali metal salts such as calcium or magnesium salts; ammonium salts; aliphatic amine salts such as trimethylamine, triethylamine, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine or procaine salts; aralkyl amine salts such as N,N-dibenzylethylonediamine salts; heterocyclic aromatic amine salts such as pyridine salts, methyl pyridine salts, quinoline salts or isoquinoline salts; quaternary ammonium salts such as tetramethylammonium salts, tetraethylammonium salts, benzyltrimethylammonium salts, benzyltriethyl-ammonium salts, benzyltributylammonium salts, methyltrioctylammonium salts or tetrabutylammonium salts, and basic amino acid salts such as arginine salts or lysine salts.

Preferably, tenofovir is in not in the form of a pharmaceutically acceptable salt, i.e. neither in the form of an acid addition salt nor in the form of a basic addition salt.

Further, it is preferred that tenofovir is present in a non-solvated/non-hydrated form.

In a preferred embodiment of the present invention all numbers referring to the weight (mg) or weight-% of tenofovir are based on the weight of tenofovir in its free form.

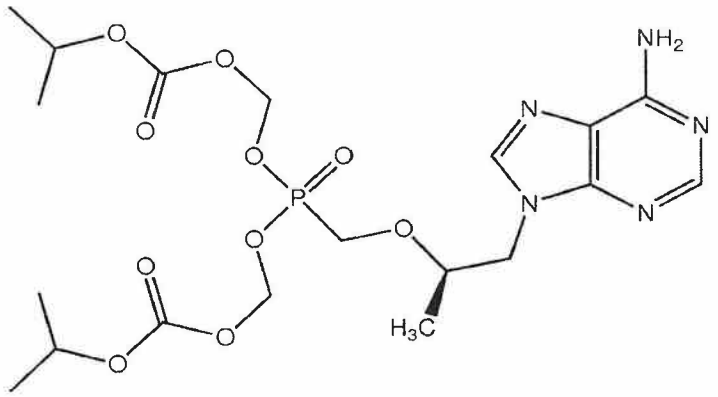
In the combination for use as a medicament of the present invention, tenofovir as

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the active ingredient can be provided in amorphous form, in crystalline form or as a mixture of both forms. Preferably, tenofovir is present in crystalline form.

In a preferred embodiment tenofovir is used in form of a prodrug of tenofovir, preferably as tenofovir disoproxil, or pharmaceutically acceptable salts thereof like e.g. tenofovir disoproxil fumarate, tenofovir alafenamide and/or hexadecyloxypropyl tenofovir. Generally, a prodrug can be regarded as a substance that is administered to a subject (preferably a human) in a pharmacologically inactive or pharmacologically less than fully active form, and is subsequently converted in the body of the subject to an active drug, preferably through metabolic processes occurring in the body of the subject. In other words, a prodrug usually serves as a type of 'precursor' to the intended drug.

In a particularly preferred embodiment the prodrug of tenofovir is tenofovir disoproxil. The chemical name of tenofovir disoproxil is (*R*)-(((1-(6-amino-9*H*-purin-9-yl)propane-2-yloxy)methyl)phosphoryl)bis(oxy)bis(methylene) isopropyl dicarbonate and is represented by the following chemical structure:

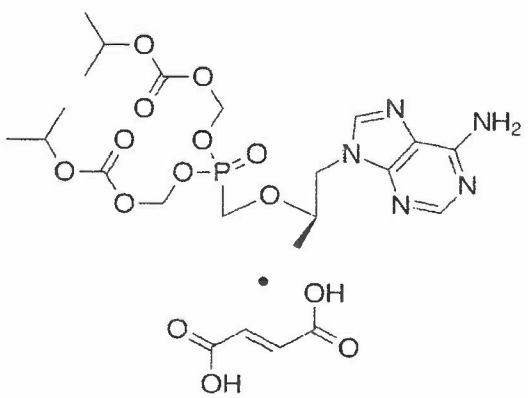


Formula (IIIa)

In this regard it is noted that in the present invention the term "tenofovir disoproxil" comprises (*R*)-(((1-(6-amino-9*H*-purin-9-yl)propane-2-yloxy)methyl)phosphoryl)-

bis(oxy)bis(methylene) isopropyl dicarbonate according to Formula (IIIa). In addition, the term "tenofovir disoproxil" comprises all the pharmaceutically acceptable salts, hydrates and/or solvates thereof. Tenofovir disoproxil and its preparation is inter alia described in EP 0 915 894 B1.

Acids which are used to prepare pharmaceutically acceptable acid addition salts are preferably those which form non-toxic acid addition salts. In a particularly preferred embodiment tenofovir disoproxil is present in form of its hemifumarate or fumarate, especially its fumarate. Tenofovir disoproxil fumarate is also known as 9-[(R)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy]-phosphinyl]methoxy]propyl]adenine fumarate (1:1) (IUPAC) and is represented by the following chemical structure:



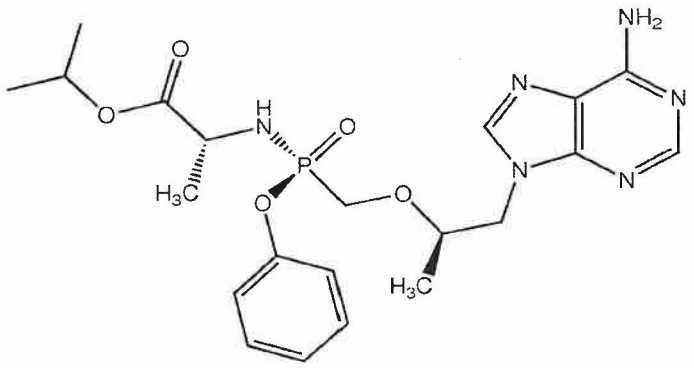
Formula (IIIb)

In a preferred embodiment of the present invention all numbers referring to the weight (mg) or weight-% of tenofovir disoproxil are based on the weight of tenofovir disoproxil fumarate.

In an alternative particularly preferred embodiment the prodrug of tenofovir is tenofovir alafenamide, also known as GS 7340. The chemical name of tenofovir alafenamide is (R)-isopropyl 2-((S)-(((R)-1-(6-amino-9H-purin-9-yl)propan-2-yloxy)methyl)(phenoxy)phosphorylamino)propanoate. Tenofovir alafenamide is

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also known as L-Alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester and is represented by the following chemical structure:



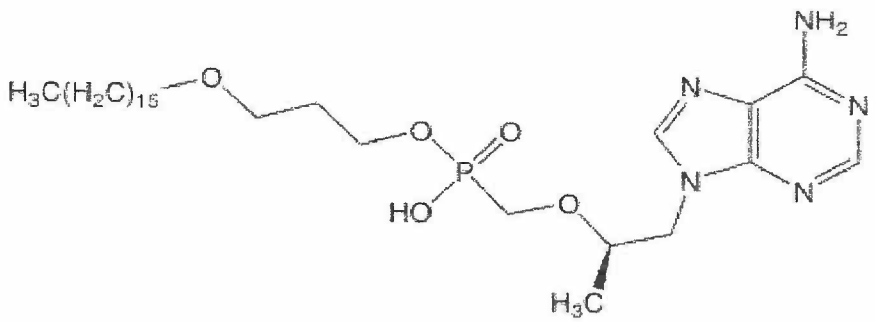
Formula (IIIc)

In this regard it is noted that in the present invention the term "tenofovir alafenamide" comprises (*R*)-isopropyl 2-((*S*)-(((*R*)-1-(6-amino-9*H*-purin-9-yl)propane-2-yloxy)methyl)(phenoxy)phosphorylamino)propanoate according to Formula (IIIc). In addition, the term "tenofovir alafenamide" comprises all the pharmaceutically acceptable salts, hydrates and/or solvates thereof. Tenofovir alafenamide and its preparation are inter alia described in WO 2013/025788 A1.

Acids which are used to prepare pharmaceutically acceptable acid addition salts are preferably those which form non-toxic acid addition salts. In a particularly preferred embodiment tenofovir alafenamide is present in form of its hemifumarate or fumarate, especially its hemifumarate.

In a preferred embodiment of the present invention all numbers referring to the weight (mg) or weight-% of tenofovir alafenamide are based on the weight of tenofovir alafenamide as free base.

In an alternative particularly preferred embodiment the prodrug of tenofovir is hexadecyloxypropyl tenofovir, also known as CMX157. The chemical name of hexadecyloxypropyl tenofovir is 3-(hexadecyloxy)propyl hydrogen ((*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yloxy)methyl)phosphonate. Hexadecyloxypropyl tenofovir is also known as hexadecyloxypropyl-9-(*R*)-[2-(phosphonomethoxy)propyl] adenine and is represented by the following chemical structure:



Formula (IIId)

In this regard it is noted that in the present invention the term "hexadecyloxypropyl tenofovir" comprises (3-(hexadecyloxy)propyl hydrogen ((*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yloxy)methyl)phosphonate according to Formula (IIId). In addition, the term "hexadecyloxypropyl tenofovir" comprises all the pharmaceutically acceptable salts, hydrates and/or solvates thereof. "Hexadecyloxypropyl tenofovir" is inter alia described in WO 2011/01171 A1.

In a preferred embodiment of the present invention all numbers referring to the weight (mg) or weight-% of hexadecyloxypropyl tenofovir are based on the weight of hexadecyloxypropyl tenofovir as free base.

The combination of the present invention preferably does not show any significant pharmacokinetic interaction of dolutegravir, emtricitabine and tenofovir.

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In a particularly preferred embodiment the pharmaceutical combination of the present invention comprises dolutegravir, emtricitabine and tenofovir as the sole pharmaceutically active agents.

In a particularly preferred embodiment the pharmaceutical combination of the present invention comprises dolutegravir, emtricitabine and tenofovir in combination with further pharmaceutically active agent(s).

In other words, the combination of the present invention preferably can be referred to as a pharmaceutical composition comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir, wherein (a) dolutegravir and (b) emtricitabine are present in a specific weight ratio, for use as a medicament. A further subject of the present invention is a method for treating a viral infection, comprising administering to a subject in need thereof the pharmaceutical combination or composition of the present invention, wherein the viral infection preferably comprises an HIV-infection.

In the pharmaceutical combination of the present invention the weight ratio of (a) dolutegravir to (b) emtricitabine is from 1 : 1 to 1 : 3, preferably from 1 : 1.2 to 1: 2.8, more preferably 1 : 1.5 to 1 : 2.5.

In a particularly preferred embodiment the weight ratio of (a) dolutegravir to (b) emtricitabine can be 1 : 2.

In the pharmaceutical combination of the present invention the weight ratio of (a) dolutegravir to (c) tenofovir may depend on the type of tenofovir prodrug and/or salt.

In case dolutegravir (in free form) and tenofovir disoproxil is used, the weight ratio of dolutegravir to (c) tenofovir disoproxil usually might be from 1 : 1.9 to 1 : 4.5, preferably 1 : 2.2 to 1 : 4.2, more preferably 1 : 2.4 to 1 : 4.

In the preferred embodiment where tenofovir disoproxil fumarate is used, the weight ratio of dolutegravir to (c) tenofovir disoproxil fumarate usually might be from 1 : 2 to 1 : 5, preferably 1 : 2.25 to 1 : 4.5, more preferably 1 : 2.5 to 1 : 4.

In a particularly preferred embodiment the weight ratio of (a) dolutegravir to (c) tenofovir disoproxil fumarate can be 1 : 3.

In an alternatively preferred embodiment the pharmaceutical combination of the present invention comprises (a) dolutegravir, (b) emtricitabine and (c) tenofovir alafenamide in which the weight ratio of (a) dolutegravir to (b) emtricitabine to (c) tenofovir alafenamide can be from 1:1:0.15 to 1:8:1, preferably from 1:2:0.16 to 1:8:0.8, and more preferably from 1:2:0.17 to 1:6:0.75, especially 1:4:0.19 to 1:4:0.60.

In a preferred embodiment of the pharmaceutical combination of the present invention the amount of dolutegravir administered is 20 to 75 mg per day, preferably 25 to 70 mg per day, more preferably 35 to 65 mg per day, in particular 40 to 60 mg per day. The amounts are based on dolutegravir in free form (not in form of a salt or a prodrug).

It is further preferred that the amount of emtricitabine administered is 50 to 150 mg per day, preferably 60 to 140 mg per day, more preferably 65 to 130 mg per day, in particular 75 to 125 mg per day. The amounts are based on emtricitabine in free form (not in form of a salt or a prodrug).

It is further preferred that the amount of tenofovir administered preferably is 5 to 300 mg per day, more preferably 7.5 to 250 mg per day, even more preferably 30 to 200 mg per day, in particular 40 to 175 mg per day. The amounts are based on tenofovir in free form (not in form of a salt or a prodrug).

In a preferred embodiment tenofovir is used in the form of tenofovir disoproxil fumarate. It is further preferred that the amount of tenofovir disoproxil fumarate

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administered preferably is 100 to 250 mg per day, more preferably 110 to 225 mg per day, even more preferably 120 to 200 mg per day, in particular 125 to 175 mg per day.

In case that the tenofovir is administered as tenofovir alafenamide, the amount of tenofovir alafenamide administered preferably is 0.5 to 50 mg per day, more preferably 1 to 45 mg per day, even more preferably 3 to 44 mg per day, in particular 5 to 42 mg per day.

As can be seen from above, the total amount of dolutegravir, emtricitabine and tenofovir disoproxil fumarate comprised in the present pharmaceutical combination for use as a medicament is between 170 and 475 mg per day, in particular 240 to 360 mg per day.

As can be seen from the above, the total amount of dolutegravir, emtricitabine and tenofovir alafenamide comprised in the present pharmaceutical combination for use as a medicament is between 70.5 and 425 mg per day, in particular 192 to 326 mg per day.

In one embodiment, the pharmaceutical combination for use as a medicament is administered via oral administration. In alternative embodiments it is preferred that the pharmaceutical combination for use as a medicament is administered per injection or infusion, e.g. intravenous, subcutaneously or intramuscular. In such a case the APIs can for example be embedded in a (degradable) biopolymer such as a polysaccharides, lipids and fibres.

In another particularly preferred embodiment, the combination of the present invention is administered once daily. Alternatively, a twice or three times daily administration can be applied.

Generally, the combination of the present invention is suitable for treating any human being having an HIV infection. In a further preferred embodiment the

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combination of the present invention is used for treating a HIV infection in human patients of the HLA-B 5701 genotype. HLA-B (major histocompatibility complex, class I, B) is a human gene that provides instructions for producing a protein that plays a critical role in the immune system. Among humans with HIV infection, a version of HLA-B designated HLA-B*5701 can be treated beneficially.

Further, in a preferred embodiment the combination of the present invention is used for treating HIV in patients suffering from swallowing disorders. Swallowing disorders (dysphagia) can result from congenital abnormalities, structural damage, and/or medical conditions. Swallowing problems are a common complaint among older individuals, and the incidence of dysphagia is higher in the elderly, in patients who have had strokes, and in patients who are admitted to acute care hospitals or chronic care facilities. Thus, in a preferred embodiment the combination of the present invention is used for treating HIV in patients being older than 50 years, in particular older than 60 years, e.g. 60 to 90 years. In another preferred embodiment the present invention is used to treat patients younger than 15 years, in particular younger than 14 years, e.g. 5 to 13 years.

A further subject of the present invention is a pharmaceutical composition comprising the combination of the present invention, i.e. a pharmaceutical composition comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir and optionally pharmaceutical excipients.

In a preferred embodiment the pharmaceutical composition comprises

(i) 20 to 75 mg, preferably 25 to 70 mg, more preferably 35 to 65 mg, in particular 40 to 60 mg dolutegravir (a);

(ii) 50 to 150 mg, preferably 60 to 140 mg, more preferably 65 to 130 mg, in particular 75 to 125 mg emtricitabine (b);

(iii) 100 to 250 mg, more preferably 110 to 225 mg, even more preferably 120 to 200 mg, in particular 125 to 175 mg tenofovir (c), in particular tenofovir disoproxil fumarate; and

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(iv) pharmaceutical excipients.

In a preferred embodiment the pharmaceutical composition comprises

(i) 20 to 75 mg, preferably 25 to 70 mg, more preferably 35 to 65 mg, in particular 40 to 60 mg dolutegravir (a);
(ii) 50 to 300 mg, preferably 100 to 280 mg, more preferably 125 to 260 mg, in particular 150 to 250 mg emtricitabine (b);
(iii) 0.5 to 50 mg, more preferably 1 to 45 mg, even more preferably 3 to 44mg, in particular 5 to 42 mg tenofovir (c), in particular tenofovir alafenamide; and
(iv) pharmaceutical excipients.

In a preferred embodiment the pharmaceutical composition of the present invention comprises

50 mg dolutegravir, 50 mg emtricitabine and 150 mg tenofovir (c), in particular tenofovir disoproxil fumarate, or
50 mg dolutegravir, 100 mg emtricitabine and 150 mg tenofovir (c), in particular tenofovir disoproxil fumarate, or
50 mg dolutegravir, 150 mg emtricitabine and 150 mg tenofovir (c), in particular tenofovir disoproxil fumarate, or
25 mg dolutegravir, 100 mg emtricitabine and 250 mg tenofovir (c), in particular tenofovir disoproxil fumarate, or
25 mg dolutegravir, 100 mg emtricitabine and 200 mg tenofovir (c), in particular tenofovir disoproxil fumarate, or
25 mg dolutegravir, 100 mg emtricitabine and 150 mg tenofovir (c), in particular, tenofovir disoproxil fumarate.

In an alternatively preferred embodiment the pharmaceutical composition of the present invention comprises

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about 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir (c), in particular tenofovir alafenamide, or
about 25 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir (c), in particular tenofovir alafenamide, or
about 50 mg dolutegravir, about 100 mg emtricitabine and about 25 mg tenofovir (c), in particular tenofovir alafenamide, or
about 50 mg dolutegravir, about 200 mg emtricitabine and about 10 mg tenofovir (c), in particular tenofovir alafenamide, or
about 50 mg dolutegravir, about 100 mg emtricitabine and about 10 mg tenofovir (c), in particular tenofovir alafenamide,
wherein the amount of tenofovir alafenamide is based of tenofovir alafenamide free base or tenofovir alafenamide hemifumarate.

In a preferred embodiment the term "about" indicates that the corresponding value can vary plus/minus 10%, in particular plus/minus 5%.

For the foregoing embodiments, each embodiment disclosed herein is contemplated as being applicable to each of the other disclosed embodiments. For example, the explanation given above for preferred embodiments of the combination or for each of the drugs of the combination also applies to the composition of the present invention.

In a preferred embodiment the pharmaceutical composition can preferably comprise one or more pharmaceutical excipient(s). The pharmaceutical excipients are excipients with which the person skilled in the art is familiar, such as those which are described in the European Pharmacopoeia (Ph.Eur.) and/or in the US Pharmacopoeia (USP).

Examples of suitable pharmaceutical excipients are glidants (d), fillers (e), disintegrants (f), binders (g), lubricants (h) and surfactants (j).

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Glidants (d) can be used to improve the flowability. For example, talc can be used as glidant. More preferably, colloidal silicon dioxide (for example Acrosil®) is used. Preferably, the glidant can be present in an amount of up to 3 wt%, preferably in amount of 0.05 to 2.5 wt%, more preferably 0.1 to 2.0 wt%, in particular 0.2 to 1.5 wt% based on the total weight of the oral dosage form. Preferably, the colloidal silicon dioxide has a specific surface area of 50 to 400 m^2/g, measured by gas adsorption according to Ph. Eur., 6.0, Chapter 2.9.26.

Fillers (e) can be used to increase the bulk volume and weight to a limit at which a dosage form can be formed. Fillers may fulfil several requirements, such as being chemically inert, non-hygroscopic, biocompatible, easily processable and may possess good biopharmaceutical properties. Preferred fillers are for example lactose, sucrose, glucose, mannitol, maltodextrin, dextrin, dextrose, hydrogenated vegetable oil and/or cellulose derivatives, such as microcrystalline cellulose and silicified microcrystalline cellulose, and mixtures thereof. More preferred are lactose, mannitol, microcrystalline cellulose and silicified microcrystalline cellulose, particularly lactose, microcrystalline cellulose and silicified microcrystalline cellulose, especially microcrystalline cellulose.

The fillers can be present in the oral dosage form of the present invention in an amount of 5 to 35 wt%, preferably 8 to 30 wt%, more preferably 12 to 20 wt% and still more preferably 10 to 15 wt% of the total weight of the dosage form.

Disintegrants (f) are reported to be compounds which can enhance the ability of the intermediate to break into smaller fragments when in contact with a liquid preferably water. Preferred disintegrants are sodium carboxymethyl starch (croscarmellose sodium) cross-linked polyvinylpyrrolidone, sodium carboxymethyl glycolate, swelling polysaccharides, for example soy polysaccharide, carrageenan, agar, pectin, starch and derivatives thereof, proteins, for example formaldehyde-casein, sodium bicarbonate or mixtures thereof.

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Disintegrants can be present in an amount of 0 to 15 wt%, preferably 1 to 12 wt%, more preferably 2 to 10 wt% and still more preferably 3 to 6 wt%, based on the total weight of the dosage form.

Binders (g) or adhesives are reported to be substances that ensure that granulates or tablets can be formed with the required mechanical strength. Binders can be for example starch, sucrose, gelatine, polyvinylpyrrolidone, cellulose derivatives, such as hydroxypropyl methylcellulose, or mixtures thereof. Binders can preferably be present in amounts of 1 to 10 wt%, preferably of 2 to 5 wt%, in particular of 2.5 to 4.5 wt% based on the total weight of the dosage form.

Lubricants (h) are generally used in order to reduce sliding friction. In particular, the intention is to reduce the sliding friction found during tablet pressing between the punch moving up and down in the die and the die wall on the one hand and between the edge of the tablet and the die wall on the other hand. Suitable lubricants are for example stearic acid, adipic acid, sodium stearyl fumarate and/or magnesium stearate. Preferably, lubricants can be present in an amount of 0 to up to 3 wt%, more preferably of 0.1 to 2.5 wt%, in particular of 0.2 to 2 wt% based on the total weight of the dosage form.

Surfactants (j) can preferably be substances which lower the surface tension or the interfacial tension between two phases, thus enabling or supporting the formation of dispersions or working as a solubilizer. Surfactants can preferably be present in amounts of 0.3 to 5 wt%, preferably of 0.5 to 4 wt%, in particular of 1 to 3 wt% based on the total weight of the dosage form.

In this regard it is generally noted that due to the nature of pharmaceutical excipients it cannot be excluded that a certain compound meets the requirements of more than one of the components (d) to (j).

In a preferred embodiment the pharmaceutical composition of the present invention can be considered as a unit dosage form comprising

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(i) 20 to 75 mg dolutegravir,
(ii) 50 to 150 mg emtricitabine,
(iii) 0.5 to 400 mg tenofovir or a prodrug thereof and optionally
(iv) pharmaceutical excipient(s).

The pharmaceutical composition of the present invention can be preferably a solid oral dosage form. It is further preferred that the dosage form of the invention is a capsule or a tablet, in particular a tablet.

A further subject of the present invention is a kit for the treatment of a viral infection, in particular an HIV-infection, comprising

(i) 20 to 75 mg dolutegravir,
(ii) 50 to 150 mg emtricitabine,
(iii) 0.5 to 400 mg tenofovir or a prodrug thereof.

This invention is illustrated by the following examples.

EXAMPLES

Antiviral Activity

The antiviral activity of the different combinations of pharmaceutically active agents was determined using cell from CEM-M7 cell line. The CEM-M7 cell line was a suspension T-cell line and expressed CD4, CXCR4 and CCR5 and was stably transduced with a long terminal repeat (LTR)-luciferase and LTR-green fluorescent protein cassette. The viral protein Tat was expressed after infection and integration of the HIV provirus into the genome of the host cell. HIV-1 transcription and expression of luciferase (CEM-M7) from the LTR promoter (viral promoter) were activated by the viral Tat protein. Therefore, luciferase activities determined three days post infection were directly proportional to the infection rates of the virus.

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The experiments were carried out with HIV-1 NL4-3 wt virus and HIV-1 R263K virus which carries a mutation in the integrase gene rendering it resistant against dolutegravir. HIV-1 NL4-3 and HIV-1 R263K virus stock were generated by transient transfection of 293T cells with proviral DNA. Virus was harvested 2 days later, aliquoted and frozen at -80°C. The infectivity of virus stocks was determined by infecting CEM-M7 cells with serial virus dilutions and determining the luciferase activities 3 days later.

The antiviral compounds were stored and freshly dissolved before each experiment. To determine the antiviral activity of the compounds or combinations thereof, a total number of 1.5 x 10^5 CEM-M7 cells were seeded in 150 µl medium in V-shaped microtiter plates. The respective dilutions of the antiviral compounds were prepared in PBS (7 dilutions and controls). Then, 10 µl of each compound or buffer controls were added to the cells. After an incubation time of 30 minutes, cells were infected with HIV-1 NL4-3 wt and HIV-1 R263K variant in a final volume of 200 µl.

Luciferase activities are shown as relative light units per second (RLU/s) which were derived from triplicate infections minus background activities derived from uninfected cells. The luciferase assay was performed as mentioned by the manufacturer (Luciferase Assay System, Promega, E1501) and quantified using an Orion Microplate Luminometer (Berthold). Raw data were exported to Excel and % infection rates were calculated. Graphs were created using GraphPad Prism. IC50 values were calculated by GraphPad Prism. The calculation of additive and synergistic effects was performed with the software *computer language R* as mentioned in the description from S. Loewe (Loewe 1953) by creating isobolograms. This analysis was performed in collaboration with the *Applied Bioinformatics Group* from Ulm University (PD Dr. Hans Kestler, Johann Kraus).

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The following compounds were tested at the indicated mass ratios:
References:

1. Combination known as Trii-572:
Dolutegravir/lamivudine/abacavir (50 mg / 300 mg / 600 mg)

2. Combination:
Dolutegravir/emtricitabine/tenofovir disoproxil fumarate (50 mg / 200 mg / 300 mg)

Combination according to the present invention:
Dolutegravir/emtricitabine/tenofovir disoproxil fumarate (50 mg / 100 mg / 150 mg)

RESULTS

The antiviral activity of dolutegravir in combination with two other antiviral drugs against HIV-1 NL4-3 wt and HIV-1 R263K was analyzed in CEM-M7 cells as mentioned above. An experiment with fixed drug combinations was performed. The drug concentrations causing 50% of the inhibition of the viral infection (IC50) were calculated using GraphPad Prism program and shown in Tables 1 and 2.

Table 1

Effect of different combinations/concentrations on WT infection

Test Drugs	Concentrations [mg]	IC50 [nm]
DLT/LMV/ACV	50/300/600	0.8
DLT/EMT/TFV	50/200/300	0.4
DLT/EMT/TFV	50/100/150	0.3

DLT corresponds to dolutegravir
LMV corresponds to lamivudine

ACV corresponds to abacavir

EMT corresponds to emtricitabine

TFV corresponds to tenofovir disoproxil fumarate

Table 2

Effects of different combinations/concentrations on R263K infection

Test Drugs	Concentrations [mg]	IC50 [nm]
DLT/LMV/ACV	50/300/600	2.3
DLT/EMT/TFV	50/200/300	0.4
DLT/EMT/TFV	50/100/150	0.3

As can be seen from the above Tables 1 and 2, despite small amounts of emtricitabine and tenofovir disoproxil fumarate the triple combination according to the present invention shows an advantageous anti-viral activity (the lower the IC50 value the better the effect) against HIV-1 NL4-3 WT and against HIV-1 R263K being resistant against dolutegravir. Further, the combination shows unexpected and significant better anti-viral activity than the combination of the product Trii-572, which is promising in clinical trials and expected to be launched in the future.

It is expected that side effects can be reduce while maintaining the desired pharmacological effect.

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Claims

1. Pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir for use as a medicament, wherein the weight ratio of (a) dolutegravir and (b) emtricitabine is from 1 : 1 to 1 : 3.

2. Pharmaceutical combination for use according to claim 1, wherein the combination is used in the treatment of viral diseases, preferably in the treatment of an HIV-infection.

3. Pharmaceutical combination for use according to claim 1 or 2, wherein dolutegravir is used in the form of the sodium salt.

4. Pharmaceutical combination for use according to any one of the preceding claims, wherein emtricitabine is used in free form.

5. Pharmaceutical combination for use according to any one of the preceding claims, wherein tenofovir is used in form of a prodrug of tenofovir.

6. Pharmaceutical combination for use according to claim 5, wherein the prodrug of tenofovir is tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide or hexadecyloxypropyl tenofovir.

7. Pharmaceutical combination for use according to claim 6, wherein the weight ratio of (a) dolutegravir and tenofovir disoproxil fumarate is from 1 : 2 to 1 : 5.

8. Pharmaceutical combination for use according to any one of the preceding claims, wherein the amount of dolutegravir administered is 20 to 75 mg per day.

9. Pharmaceutical combination for use according to any one of the preceding claims, wherein the amount of emtricitabine administered is 50 to 150 mg per day.

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10. Pharmaceutical combination for use according to any one of the preceding claims, wherein the amount of tenofovir administered is 10 to 400 mg per day.

11. Pharmaceutical combination for use according to any one of the preceding claims, wherein the amount of tenofovir diisoproxil fumarate administered is 100 to 250 mg per day.

12. Pharmaceutical combination for use according to any one of the preceding claims, wherein the combination is administered once daily.

13. Pharmaceutical composition comprising a pharmaceutical combination according to any one of claims 1 to 11, wherein the composition comprises

(i) 20 to 75 mg dolutegravir,
(ii) 50 to 150 mg emtricitabine,
(iii) 0.5 to 400 mg tenofovir or a prodrug thereof and optionally
(iv) pharmaceutical excipient(s).

14. Pharmaceutical composition according to claim 13, wherein the composition is a solid oral dosage form, preferably a tablet.

15. A kit for the treatment of a viral infection, in particular of an HIV-infection, comprising

(i) 10 to 75 mg dolutegravir,
(ii) 50 to 150 mg emtricitabine,
(iii) 0.5 to 400 mg tenofovir or a prodrug thereof.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/067305

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/513 A61K31/5365 A61K31/675 A61P31/18
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STELLBRINK H -J ET AL: "Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study", AIDS 20130717 LIPPINCOTT WILLIAMS AND WILKINS GBR, vol. 27, no. 11, 17 July 2013 (2013-07-17) , pages 1771-1778, XP055141318, ISSN: 0269-9370 abstract page 1772 ----- -/--	1-15

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 September 2014	01/10/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Opravz, Petra

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Form PCT/ISA/210 (second sheet) (April 2005)

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	"Truvada: Treatment of HIV-1 Infection", INTERNET , 7 July 2014 (2014-07-07), XP002729923, Retrieved from the Internet: URL:http://www.rxlist.com/truvada-drug/indications-dosage.htm [retrieved on 2014-09-19] the whole document -----	

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Retesting of suspected low-level HIV-1 viral load blips: A new paradigm to prevent extra clinic visits and unnecessary patient anxiety

Joe Eron, William Garner, Lilian Wei, Lijie Zhong, Michael Miller, Javier Szwarcberg, Hal Martin, Andrew Plummer, Kim Lindstrom, James Porter, David Piontkowsky, Angela Light, Heinz Reiske, Erin Quirk, and Kirsten White

ID Week
Oct 28, 2016
Abstract 948
New Orleans, LA, USA

Disclosures

- Joe Eron
  - Research support to UNC-Chapel Hill – Abbvie, Gilead Sciences, Janssen, Bristol-Myers Squibb, ViiV Healthcare
  - Consultant – Gilead Sciences, Janssen, Bristol-Myers Squibb, ViiV Healthcare
- Kirsten White, William Garner, Lilian Wei, Lijie Zhong, Michael Miller, Javier Szwarcberg, Hal Martin, Andrew Plummer, Kim Lindstrom, James Porter, David Piontkowsky, Erin Quirk
  - Employees and stock holders of Gilead Sciences, Inc.
- Angela Light, Heinz Reiske
  - Employees of Covance

Introduction

- Goal of HIV-1 treatment is to achieve and maintain HIV-1 RNA < 50 copies/mL
- Virologic failure leads to drug resistance and regimen change
  - Virologic failure = confirmed VL > 200 copies/mL (IAS-USA, DHHS)
- Uncertainty regarding management when HIV RNA above the limit of detection but < 200 c/mL
- Low-level virologic rebound > 50 copies/mL frequently triggers a cascade of patient management events
  - Contact patient with results which may induce provider and patient anxiety
  - Return to clinic to counsel on adherence and repeat viral load test
    - IAS-USA recommends within 4 weeks
  - Little specific guidance for persistent or repeated episodes of LLV
  - Incorporation of resistance testing?
- Assay variability vs. clinically relevant result

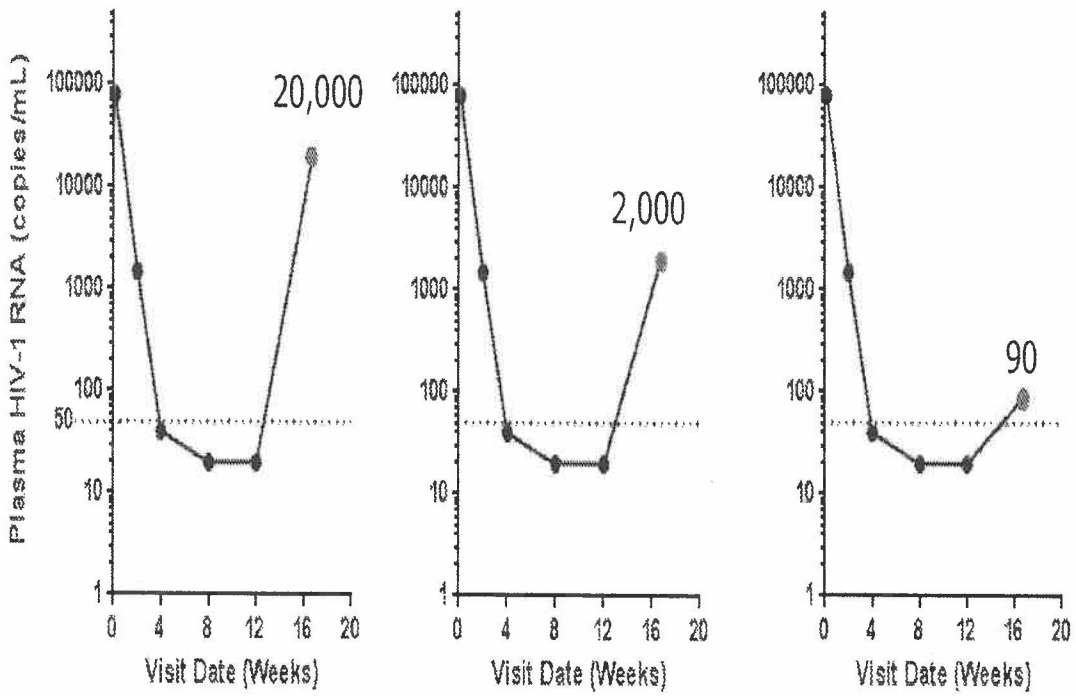
Antiretroviral Cohort Collaboration Vandenhende et al AIDS 2015, Laprise et al CID 2013, Henrich et al PLoS One 2012, Young et al BMC Infect Dis 2015, Boillat-Blanco et al Antiviral Ther 2015, **Nettles R, et al JAMA 2005**

HIV-1 Virologic Rebound Scenarios

High-level viral load rebound
- Non-adherence
- Resistance?

Intermediate viral load rebound
- Resistance?
- Non-adherence

Low-level viral load rebound
- Non-adherence?
- Resistance?
- Assay Variability?



Objectives

- Describe the natural variation of HIV-1 RNA quantification around 50 copies/mL
- Discuss clinical implications of assay variability and management of virologic failure

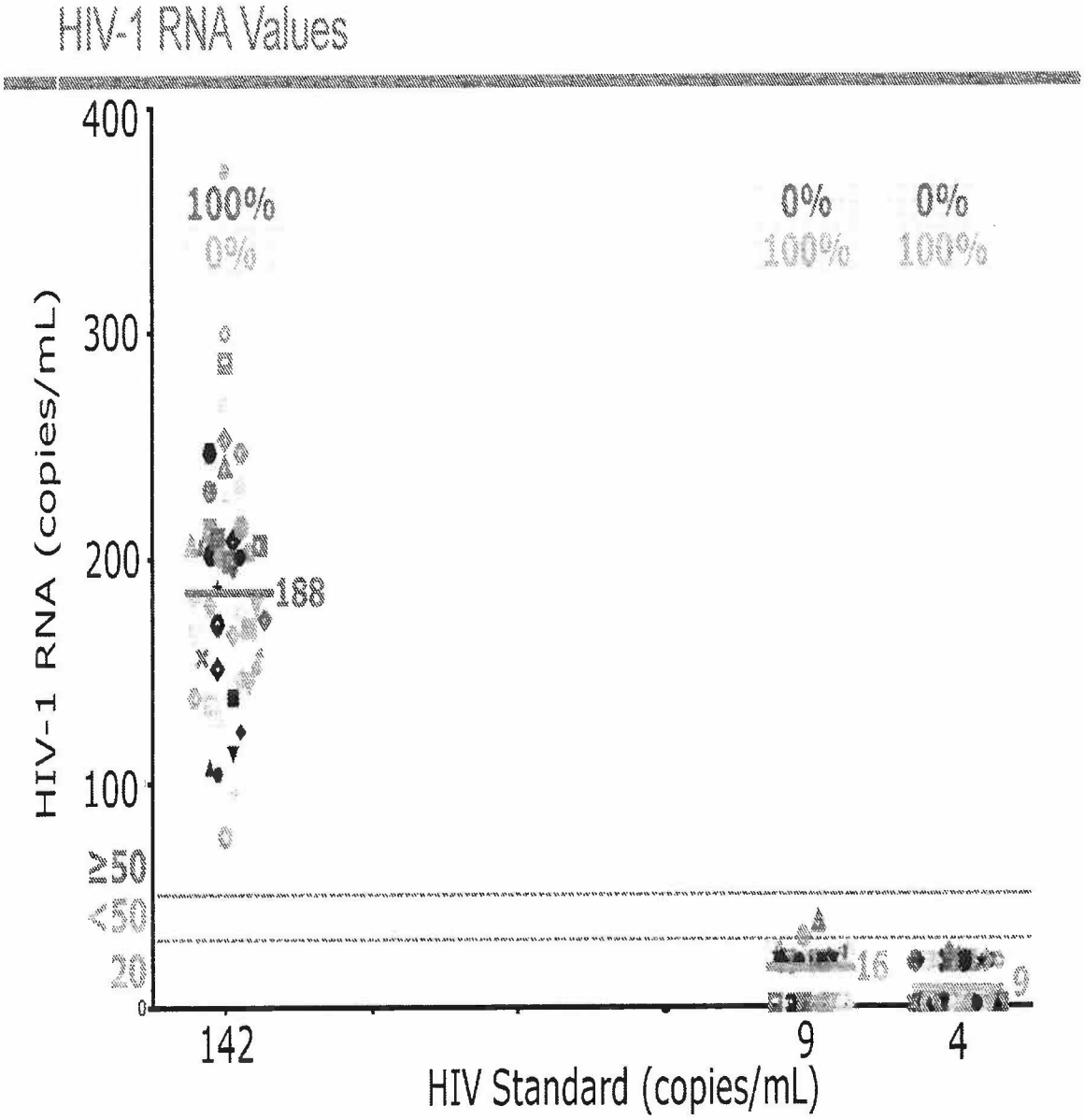
Definitions

- LLOQ = quantitative limit of an assay (e.g. < 50, < 40, < 20 etc)
- TND = target not detected – result is below the background signal in a given assay.

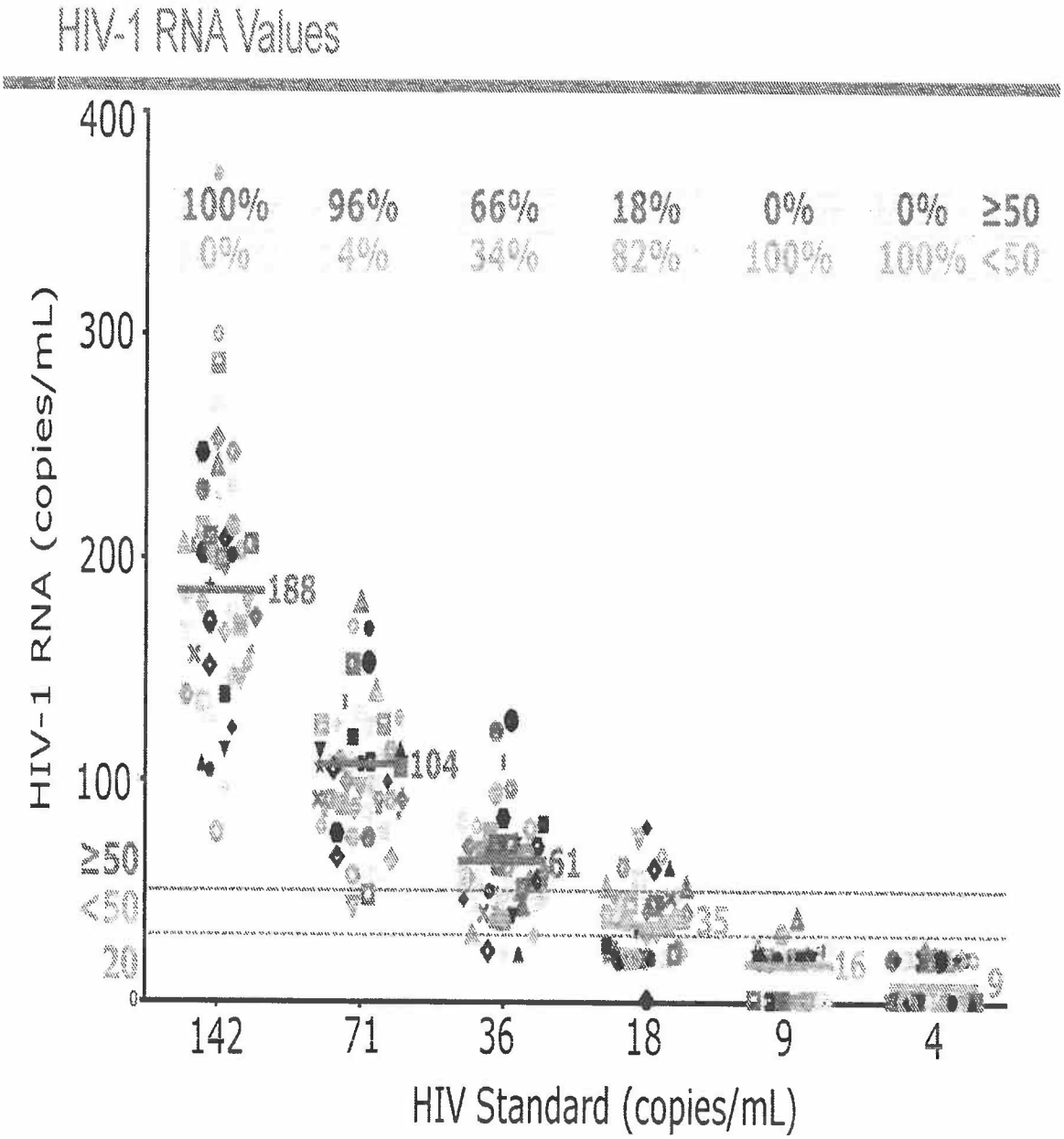
Method

- Cobas AmpliPrep/Cobas TaqMan v2.0 HIV-1 assay (Roche) was utilized
  - Quantitative values above 20 copies/mL
  - HIV-1 RNA < 20 copies/mL
  - HIV-1 RNA Target Not Detected
- Two separate evaluations were undertaken:
  - HIV-1 RNA (WHO HIV standard) was serially diluted and aliquoted into 50 tubes, frozen, and shipped to 3 Covance central laboratories with low-level viral loads targeted for testing:
    - 142, 71, 36, 18, 9, and 4 copies/mL
  - Multiple HIV-1 RNA measurements from plasma samples from five patients with multiple stored aliquots
    - 4 with rebounds ranging from 50 to 93 copies/mL
    - 1 not yet suppressed with 81 copies/mL

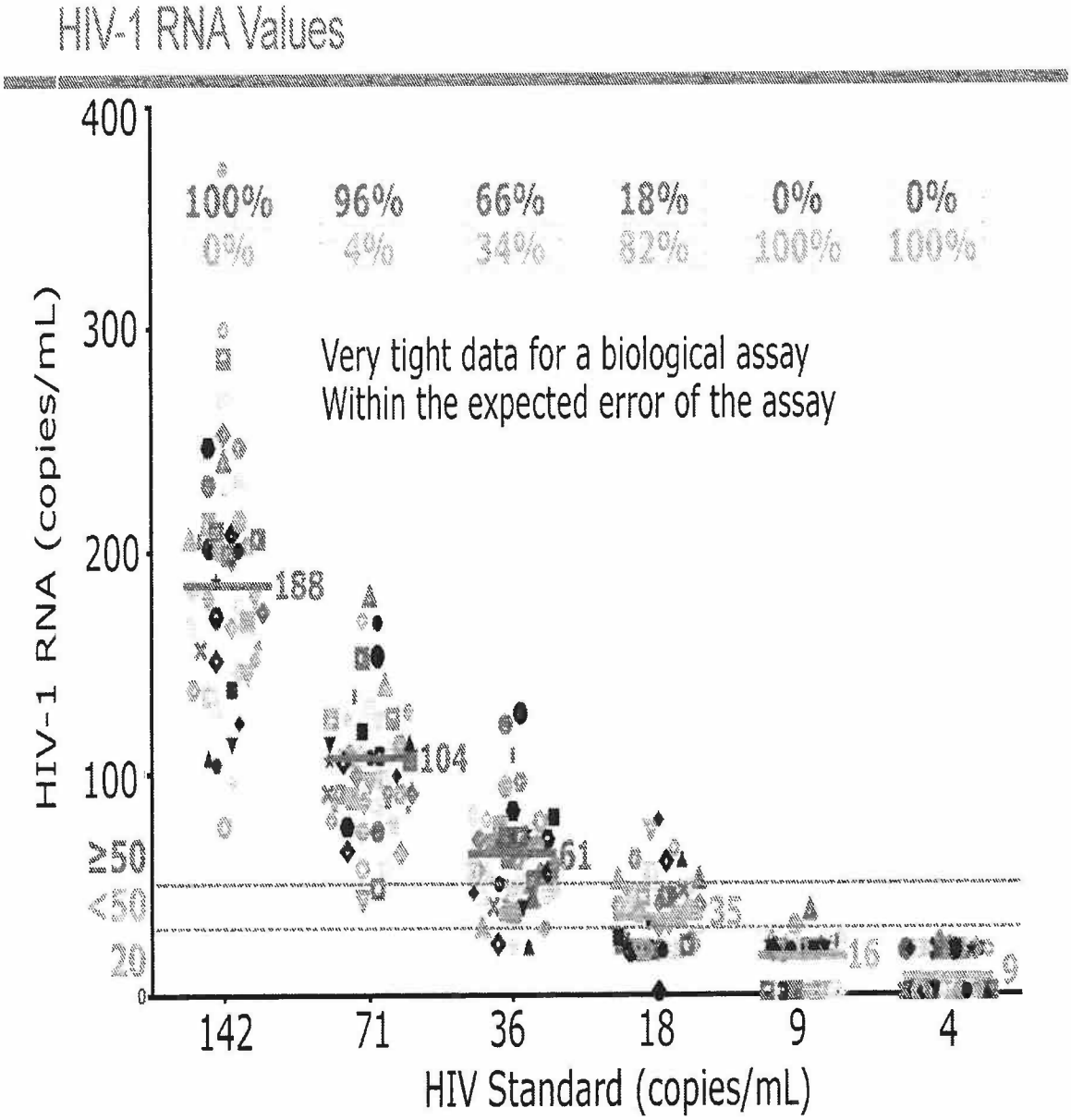
WHO Standard: 50 Replicates



WHO Standard: 50 Replicates

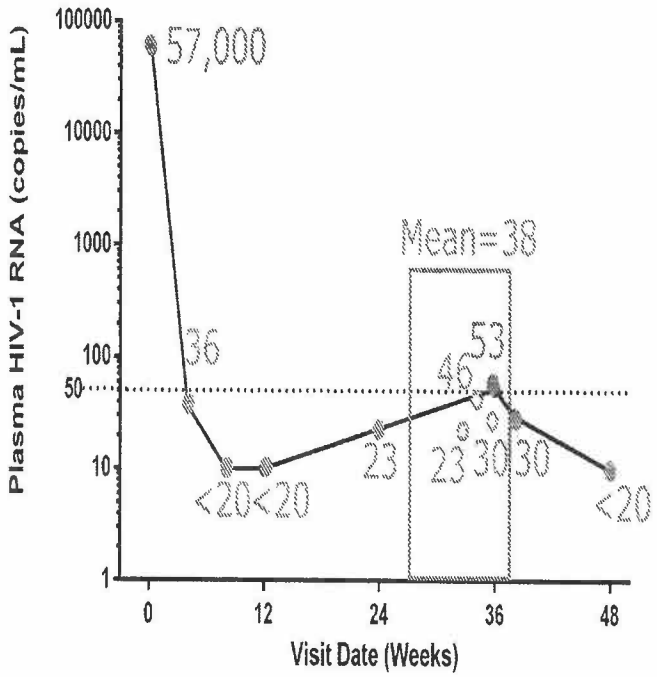


WHO Standard: 50 Replicates



Retesting of Patient Aliquots

Case 1: low-level viremia

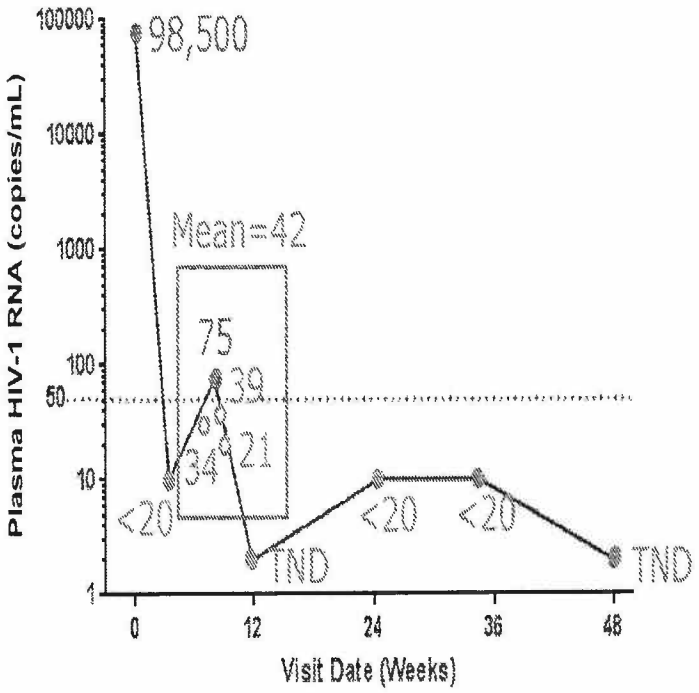


This result would likely lead to a call to the patient and repeat HIV RNA testing in 3-5 weeks

(3 repeats)

Retesting of Patient Aliquots

Case 2: low-level viremia

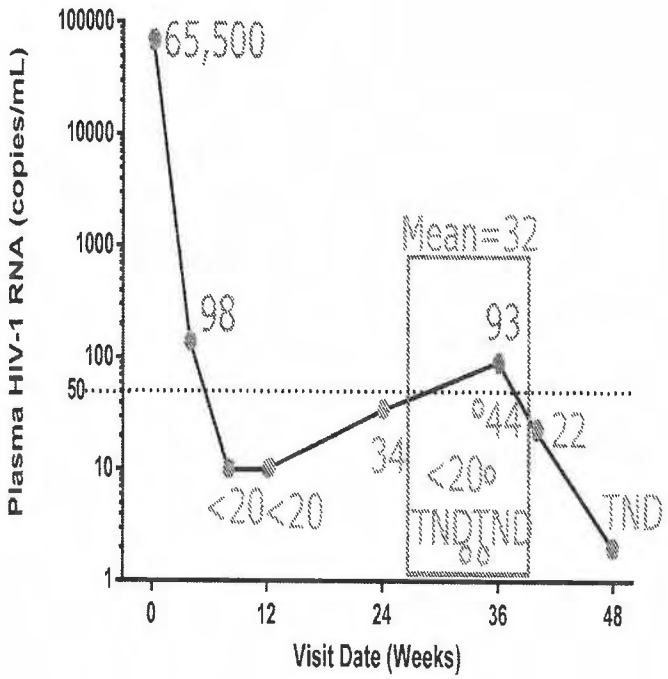


TND = HIV-1 RNA Target Not Detected

(3 repeats)

Retesting of Patient Aliquots

Case 3: low-level viremia

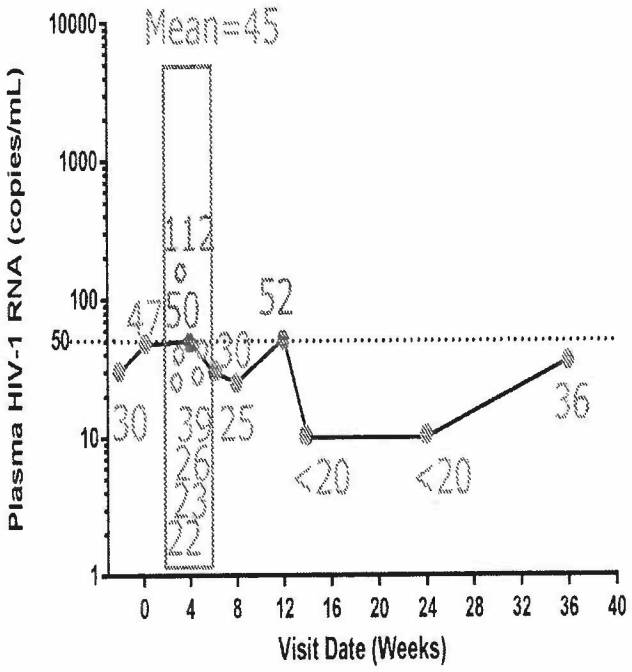


(4 replicates)

Retesting of Patient Aliquots

Case 4: low-level viremia

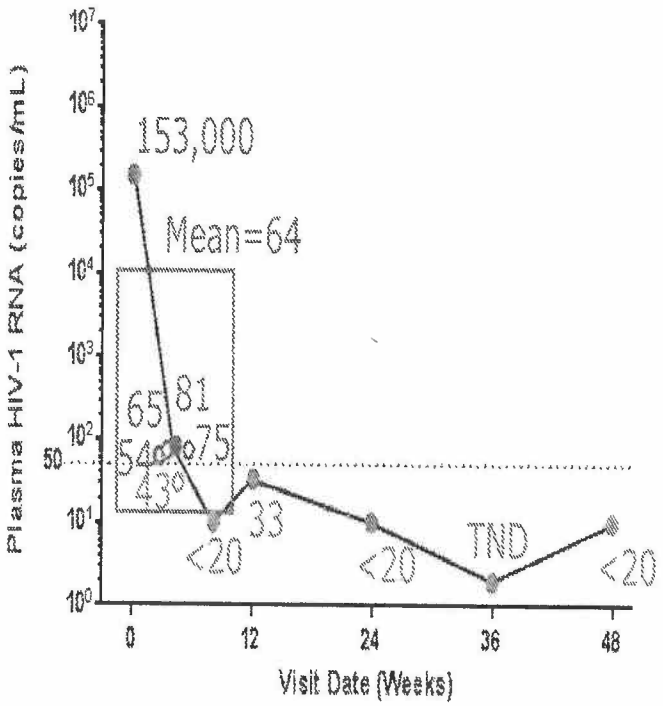
In patients with prior suppression
Same Sample retesting was <50 in 14/15 results



(5 replicates)

Retesting of Patient Aliquots

Case 5: pre-suppression low-level viremia

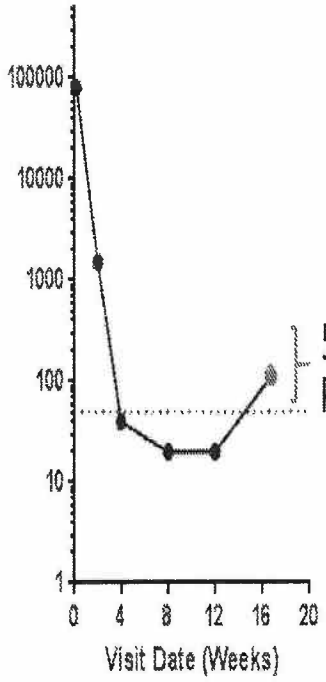


This result (HIV RNA of 81 c/mL) at 4 – 8 weeks would likely have no clinical consequences.

(4 replicates)

Repeat Testing of the Same Samples with 50-200 copies/mL

Proposed New Paradigm



50-200 copies/mL
Repeat HIV-1 RNA

Confirms >50 copies/mL
- Schedule an office visit
- Draw new blood sample for VL testing
- Collect a resistance sample

Repeat <50 copies/mL
- No new visit needed
- No further blood work needed

New FDA Guidance

Updated FDA Guidance for HIV drug development trials allows for retesting of the **same** sample for determining virologic success

For the FDA Snapshot analysis, "virologic outcome should be determined **by the last available measurement** while the patient is on treatment and continued on trial within the time window..., **even if an aliquot from the same sample was retested.**"

Reference: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry
U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER)
November 2015 Clinical/Antimicrobial Revision 1

Conclusions

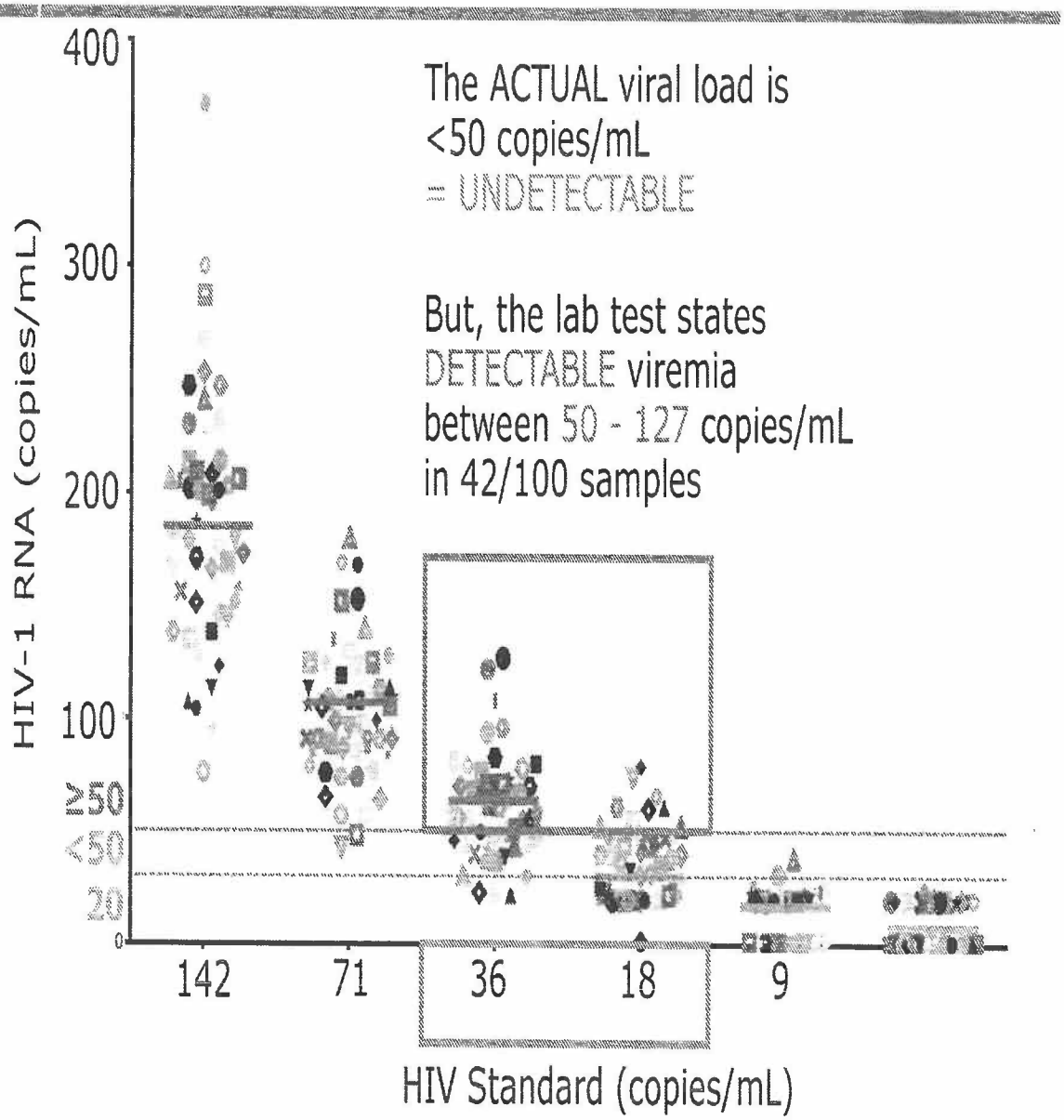
- There is biological and laboratory variation of HIV-1 RNA quantification around 50 copies/mL
  - 18% results >50 copies/mL when actual viral load is 18 copies/mL
  - 14/15 patient retest samples of post-suppression low-level viremia were <50 copies/mL
- HIV researchers, guidelines and clinicians should discuss clinical implications of assay variability and management of virologic failure
- With same sample retesting for HIV RNA above LLOQ clinician response and patient follow-up could be simplified
  - If NOT confirmed and retest value <50 copies/mL, this prevents additional clinical visits, blood draws, laboratory tests and patient anxiety
  - If confirmed > 50 copies/mL with repeat testing, do contact patient and schedule a new office visit
- Implementation of same sample retesting will require banking of samples; reflex testing by testing centers could be envisioned

Acknowledgements

- Patients who participated in this study
- Sites and study management staff

WHO Standard: 50 Replicates

HIV-1 RNA Values



PW-030
Sunday-415

Novel Integrase Strand Transfer Inhibitor Bictegravir 10 Day Monotherapy in HIV-1–Infected Patients

Joel Gallant,[1] Melanie Thompson,[2] Edwin DeJesus,[3] Gene Voskuhl,[4] Xuelian Wei,[5] Julia Zack,[5] Kirsten White,[5] Hal Martin,[5] Javier Szwarcberg[5]

[1]Southwest CARE Center, Santa Fe, NM; [2]AIDS Research Consortium of Atlanta, GA; [3]Orlando Immunology Center, Orlando, FL; [4]AIDS Arms, Inc., Dallas, TX; [5]Gilead Sciences, Inc., Foster City, CA

ASM Microbe 2016

Introduction

- Integrase strand transfer inhibitors (INSTIs) are a recommended class of antiretrovirals (ARVs) for treatment of HIV-1 in treatment guidelines[1,2]
- Three INSTIs are currently approved: raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG)
  - RAL requires twice-daily administration, and EVG requires pharmaco-enhancement for once-daily dosing, which creates more potential drug-drug interactions
  - RAL and EVG have overlapping resistance profiles
  - DTG is an unboosted INSTI that can be administered once daily
  - While DTG retains activity against most RAL- and EVG-resistant variants, it must be dosed twice daily in patients with known or suspected INSTI resistance, or when coadministered with cytochrome P450 or uridine diphosphate glucuronosyltransferase inducers

1. EACS Guidelines 8.0. http://www.eacsociety.org/files/2015_eacsguidelines_8_0-english_rev-20160124.pdf. October 2015;
2. Panel on Antiretroviral Guidelines for Adults and Adolescents.
http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Jan 28, 2016.

Introduction (continued)

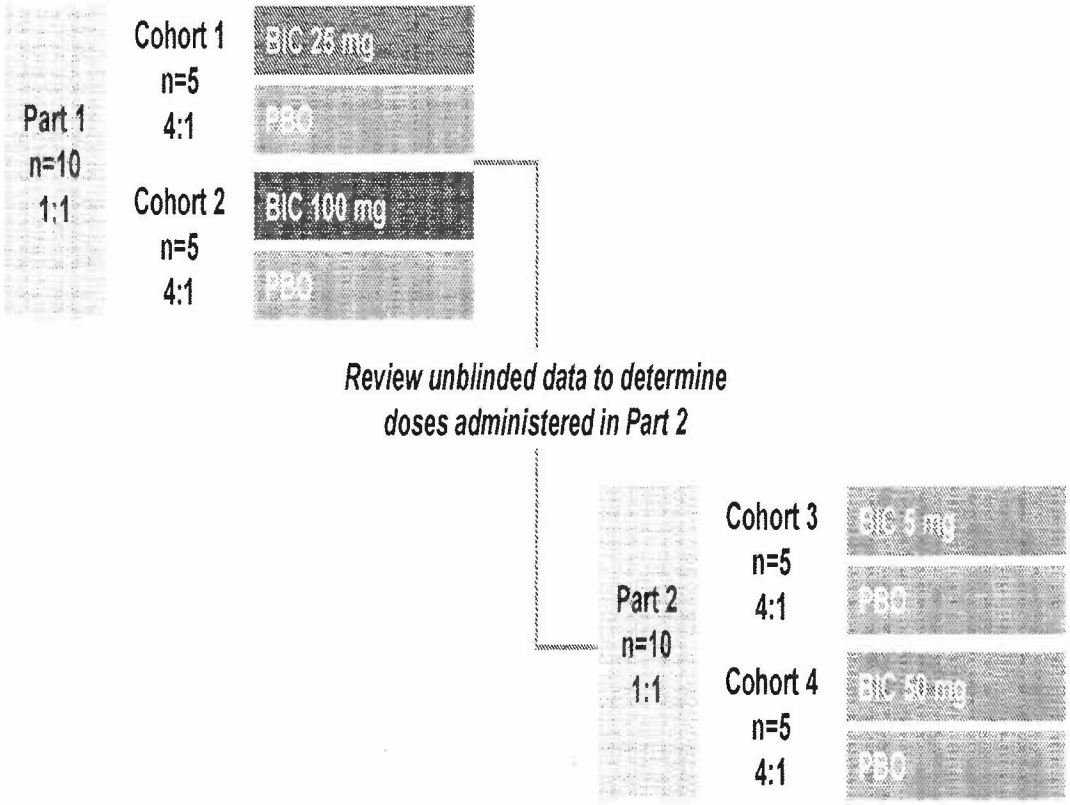
- Bictegravir (BIC; GS-9883) is a novel, potent, once-daily, unboosted INSTI with in vitro activity against most INSTI-resistant variants
- BIC is currently in clinical development in combination with tenofovir alafenamide and emtricitabine as a single-tablet regimen for the treatment of HIV-1 infection[1-4]

1. Jones G, et al. ASM Microbe 2016, poster 1673; 2. Lazerwith SE, et al. ASM Microbe 2016, poster 414; 3. Tsiang M, et al. ASM Microbe 2016, poster 1643; 4. White K, et al. 14th European Meeting on HIV & Hepatitis 2016, abstr O-01.

Objectives

- To evaluate the short-term antiviral potency of BIC compared with placebo (PBO) once daily for 10 days at doses ranging from 5 to 100 mg in HIV-infected adults
- To characterize the pharmacokinetics (PK) of BIC following multiple daily doses in HIV-1-infected patients
- To characterize the dose-response relationship between BIC exposure and viral dynamics of HIV-1
- To assess for emergence of INSTI resistance mutations during 10 days of BIC monotherapy
- To investigate the safety and tolerability of BIC at doses of 5–100 mg compared with PBO

Study Design



- This was a double-blind, adaptive, sequential-cohort, placebo-controlled study of BIC monotherapy in HIV-1–infected patients (NCT02275065)

Study Design

- Patients with chronic HIV-1 infection, HIV-1 RNA ≥10,000–≤400,000 copies/mL, and CD4 cell count >200/μL, who were ARV naive or previously treated, INSTI naive, and off of any ARV treatment for ≥12 weeks were eligible to screen
  - Patients were required to have no genotypic or phenotypic resistance to any INSTI at screening
- In Part 1, 10 patients were randomized 1:1 to Cohort 1 (BIC 25 mg) or Cohort 2 (BIC 100 mg)
  - Within each cohort, patients were assigned in a 4:1 ratio to receive active BIC or matching PBO
- Following review of data from Part 1, 10 patients were randomized 1:1 to Cohort 3 (BIC 5 mg) or Cohort 4 (BIC 50 mg)
  - Within each cohort, patients were again randomized 4:1 to receive active BIC or matching PBO

Study Design (continued)

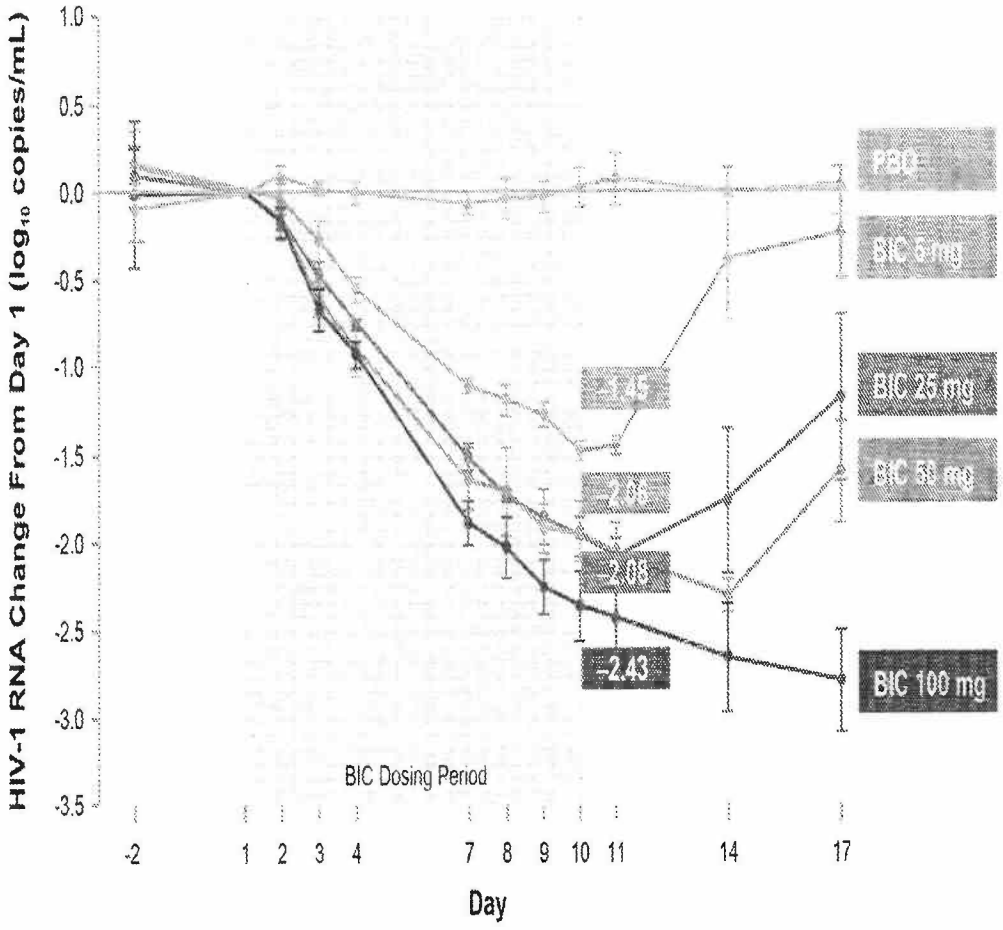
- Screening, baseline, and Day 11 samples for each patient were tested for genotypic and phenotypic resistance to reverse transcriptase, protease, and integrase (Monogram Biosciences, South San Francisco, CA)
- All patients received study medication in a fasted state for 10 days and were monitored for safety for an additional 7 days
- Virologic responses were compared between each BIC treatment group and the pooled PBO group using the t test at a 2-sided 0.05 significance level based on an analysis of variance model
- BIC PK parameters were listed and summarized by treatment group
- Safety data, including adverse events (AEs), laboratory data, and vital signs, were summarized by treatment
  - AEs were coded using MedDRA Version 17.1

Baseline Characteristics

Characteristic	BIC				PEG
	5 mg n=4	25 mg n=4	50 mg n=4	100 mg n=4	n=4
Mean age, y (range)	29 (25–34)	44 (29–59)	34 (19–44)	36 (26–48)	24 (21–28)
Male, n	4	4	3	4	4
Race, n					
White	4	2	3	3	1
Black	0	1	1	1	3
Mean BMI, kg/m^2 (SD)	27.5 (5.35)	26.9 (2.23)	22.5 (3.64)	27.4 (3.84)	22.7 (2.45)
Mean HIV-1 RNA, log_{10} copies/mL (SD)	3.8 (1.02)	4.6 (0.50)	4.4 (0.46)	4.7 (1.04)	4.5 (0.41)
Mean CD4 count /μL (SD)	520 (138)	329 (98)	445 (124)	410 (215)	507 (113)
ARV status, n					
ARV naive	3	3	4	2	4
ARV experienced	1	1	0	2	0

BMI, body mass index; SD, standard deviation.

Mean Change (95% confidence interval) in HIV-1RNA



Virologic Responses to Bictegravir

	BIC				
	5 mg n=3*	25 mg n=4	50 mg n=4	100 mg n=4	PBO n=4
Mean $DAVG_{11}$, log_{10} copies/mL (SD)	-0.92 (0.10)	-1.33 (0.17)	-1.37 (0.31)	-1.61 (0.26)	-0.01 (0.14)
Pairwise p-value† vs:					
PBO	<0.001	<0.001	<0.001	<0.001	
BIC 100 mg	<0.001	0.10	0.15		
Mean Δ HIV-1 RNA Day 11 from baseline, log_{10} copies/mL (SD)	-1.45 (0.10)	-2.08 (0.21)	-2.06 (0.35)	-2.43 (0.39)	0.08 (0.30)
Pairwise p-value† vs:					
PBO	<0.001	<0.001	<0.001	<0.001	
BIC 100 mg	<0.001	0.11	0.09		
Mean max reduction from baseline HIV-1 RNA, log_{10} copies/mL (SD)	-1.52 (0.08)	-2.18 (0.24)	-2.31 (0.19)	-2.91 (0.53)	-0.12 (0.18)
Pairwise p-value† vs:					
PBO	<0.001	<0.001	<0.001	<0.001	
BIC 100 mg	<0.001	0.004	0.01		
Patients ever achieving HIV-1 RNA <50 copies/mL by end of study, n (%)	0	0	1 (25)	2 (50)	0

*1 patient was excluded from virologic assessments as HIV-1 RNA on Day 1 was 173 copies/mL; †2-sided t test. DAVG11, time-weighted average change from baseline to study Day 11. max, maximum..

Summary of Bictegravir Multiple-Dose PK Parameters

	BIC			
PK Parameter	5 mg n=4	25 mg n=4	50 mg n=4	100 mg n=4
Mean AUC_{τ}, h*ng/mL (%CV)	9983 (26.7)	48,950 (40.0)	87,538 (32.7)	178,902 (17.8)
Mean C_{τ}, ng/mL %CV	225.3 (37.5)	1052.3 (54.1)	2053.0 (47.6)	4520.0 (21.9)
Median $t_{½}$, h (Q1, Q3)	20.8 (17.2, 23.8)	15.9 (14.1, 19.4)	17.8 (15.5, 20.5)	20.9 (17.9, 24.5)
Median $_{pa}$IQ 95 (range)*	1.3 (0.9–2.1)	4.9 (4.4–11.7)	13.4 (5.3–18.6)	25.9 (23.0–36.9)

*Protein-adjusted 95% inhibitory quotient ($_{pa}$IQ95) based on observed steady-state concentration at end of dosing interval (C_{τ}) and in vitro protein-adjusted 95% inhibitory concentration for wild-type HIV-1 (162 ng/mL). AUC_{τ}, area under plasma concentration–time curve for dosing interval; %CV, coefficient of variation; Q, quartile; $t_{½}$, half-life.

Safety Summary

- There were no serious AEs or AEs leading to study drug discontinuation
- Headache (1 each in 5-, 25-, and 100-mg groups) and diarrhea (1 each in 5- and 100-mg groups) were the only AEs reported in >1 patient on BIC
- Most laboratory abnormalities were Grade 1; only 2 patients had a Grade 2 abnormality:
  - 1 patient on PBO had Grade 2 amylase on Day 10
  - 1 patient in the BIC 5-mg arm had Grade 2 aspartate aminotransferase and creatine phosphokinase abnormalities on Day 17 attributed to crystal methamphetamine use

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Conclusions

- BIC 10 day monotherapy led to rapid declines in HIV-1 RNA from baseline that were sustained through the treatment period with no viral breakthrough
- HIV-1 RNA decreases demonstrated a dose-response effect, and viral rebound after the treatment period was delayed to Day 14 in the 50-mg dose group and to Day 17 in the 100-mg group
- 3 patients (1 in 50-mg arm, 2 in 100-mg arm) had HIV-1 RNA <50 copies/mL by end of study
- No primary INSTI resistance mutations were selected following 10 days of monotherapy
- BIC was well tolerated at all dose levels through 10 days of dosing
- BIC plasma exposure was linear and dose proportional at doses up to 100 mg

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Acknowledgments

We extend our thanks to the patients, investigators, and staff who participated in this study. This study was funded by Gilead Sciences, Inc.

Bictegravir (GS-9883), a Novel HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Optimized In Vitro Resistance Profile

Gregg Jones, Joshua Goldsmith, Andrew Mulato, Kirsten White, Derek Hansen, Kirsten Stray, Stephen Yant, Scott Lazerwith, Haolun Jin, Tomas Cihlar and Manuel Tsiang

Gilead Sciences, Foster City, CA

ASM Microbe
June 2016
Boston, MA
Poster #413

Introduction

- Integrase strand transfer inhibitors (INSTIs) are a class of antiretroviral drugs for the treatment of HIV-1 infection and inhibit HIV-1 replication by blocking the strand transfer step of viral DNA integration into the host genome.
- The first two INSTIs, raltegravir (RAL) dosed twice-daily and elvitegravir (EVG) dosed-once daily with boosting, are approved for clinical use as components of combination therapy. However, RAL and EVG have overlapping resistance profiles such that viruses resistant to one drug are cross-resistant to the other drug, which ultimately precludes the sequential use of these two INSTIs.
- Dolutegravir (DTG) is also an INSTI and is dosed once-daily without boosting and possesses a higher barrier to resistance development and a resistance profile distinct from that of RAL and EVG. However, DTG must be dosed twice-daily in patients with documented or suspected INSTI-associated resistance. Consequently, novel INSTIs with improved efficacy against INSTI-associated resistance are still necessary.
- Our goal was to develop a novel INSTI with once-daily dosing potential, improved tolerability, and high efficacy against INSTI-associated resistance.
- Bictegravir (BIC; GS-9883) is a novel potent once-daily unboosted INSTI currently in clinical development in combination with tenofovir alafenamide (TAF) and emtricitabine (FTC) in a single-tablet regimen for the treatment of HIV-1 infection.
- In this study, we report the antiviral potency of BIC against HIV-1 variants with resistance associated mutations and *in vitro* selection of resistant HIV-1 variants under BIC selective pressure.

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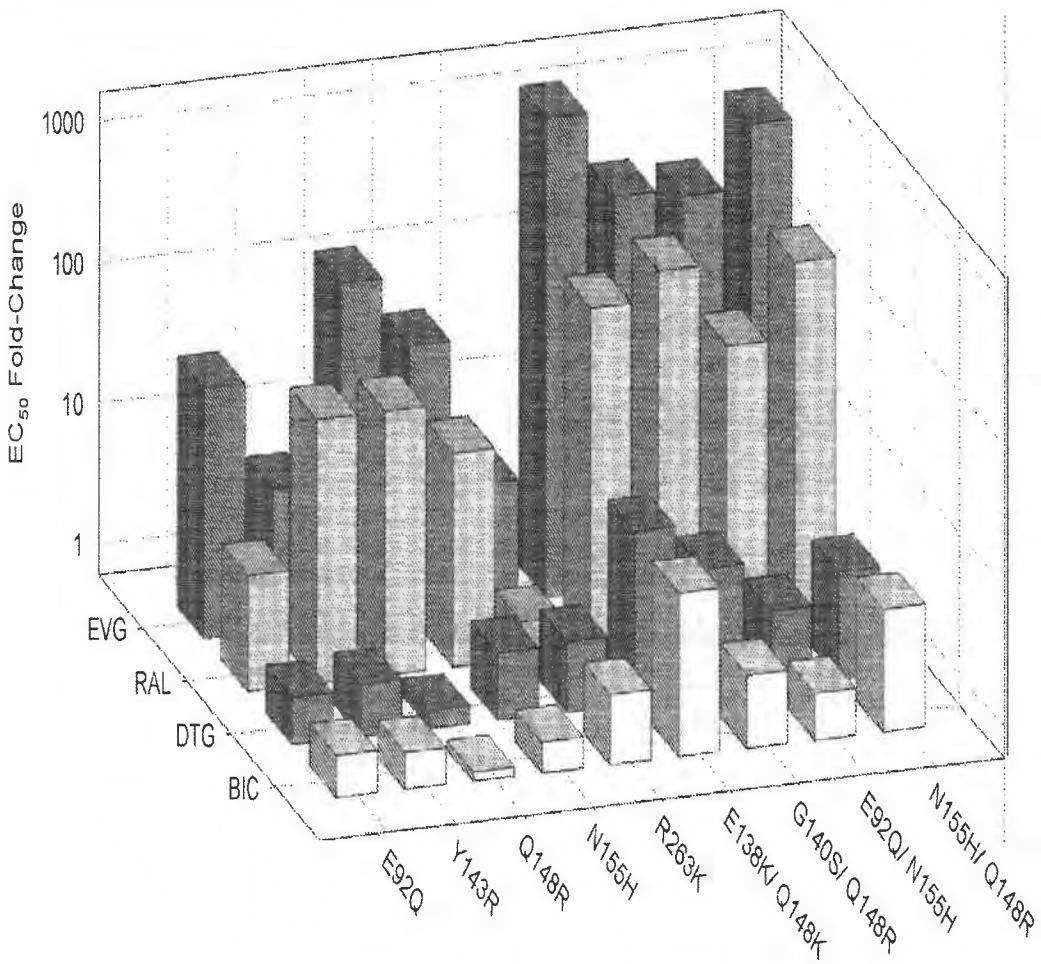
Methods

- HIV-1 site-directed mutants with either NRTI, NNRTI, PI, or INSTI resistance associated mutations were profiled for susceptibility to BIC in MT-2 cells.
- 18 clonal and 47 patient-derived HIV-1 isolates with high-level INSTI resistance were profiled for susceptibility to BIC using the PhenoSense integrase assay through a contract study with Monogram Biosciences (South San Francisco, CA).
- *In vitro* resistant variants were selected with escalating doses of BIC, DTG, and EVG, and emergent HIV-1 variants were genotyped and phenotyped.
- *In vitro* resistance breakthrough studies using clinically relevant fixed doses of BIC, EVG, and DTG were conducted in MT-2 cells and primary human $CD4^+$ T-cells.

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Results

Figure 1. Bictegravir (BIC) Has Improved Resistance Profile Compared to DTG, RAL and EVG

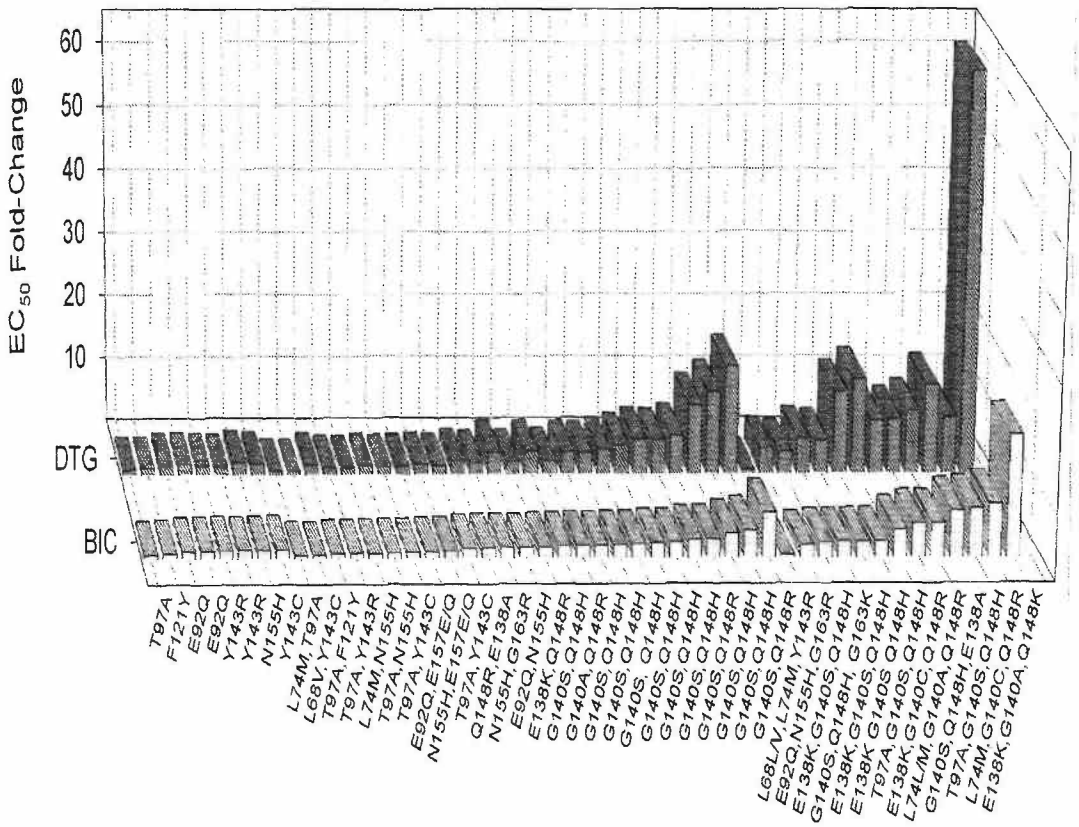


EFV (data not shown) used as a control, showed no resistance with 0.8 – 1.2-fold change in EC_{50}

4

Results

Figure 2. Bictegravir (BIC) has an Improved Resistance Profile Relative to DTG Against 47 HIV-1 Patient-derived Isolates with INSTI Resistance Mutations



The numerical data of this graph is shown in Table 1.

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Results

Table 1. Bictegravir (BIC) has an Improved Resistance Profile Relative to DTG Against 47 HIV-1 Patient-derived Isolates with INSTI Resistance Mutations

INSTI Resistance Mutations[a]	Susceptibility (Fold-change vs. WT)[b]			
	BIC	DTG	EVG	RAL
L74M,T97A	0.50	0.64	18	8.48
L68V,Y143C	0.54	0.54	1.9	4.06
L68L/V,L74M,Y143R	0.59	0.74	26	>143
T97A	0.66	0.88	10	1.78
T97A,F121Y	0.80	1.63	>150	112
T97A,Y143R	0.83	1.11	20	>143
F121Y	0.84	1.05	36	12
L74M,N155H	0.90	1.08	103	89
T97A,N155H	0.99	1.51	65	80
T97A,Y143C	1.02	1.35	29	>143
E92Q,E157E/Q	1.16	1.41	51	4.8
E92Q	1.19	1.58	60	18
N155H,E157E/Q	1.23	1.66	28	19
E92Q	1.30	1.73	61	6.7
Y143R	1.39	1.50	2.26	22
Y143R	1.39	1.40	2.19	16
N155H	1.42	2.07	>150	107
Y143C	1.49	1.76	4.24	14
T97A,Y143C	1.60	1.47	42	>143
Q148R,E138A	1.69	2.17	>150	43
N155H,G163R	1.70	1.95	21	15
E92Q,N155H	1.72	3.49	>150	>143
E138K,Q148R	1.80	2.05	>150	54
G140S,Q148H	1.99	3.60	>150	>143

INSTI Resistance Mutations[a]	Susceptibility (Fold-change vs. WT)[b]			
	BIC	DTG	EVG	RAL
E92Q,N155H,G163R	2.02	4.12	>150	>143
G140A,Q148R	2.03	2.22	>150	86
G140S,Q148H	2.03	3.52	>150	>143
G140S,Q148H	2.12	3.44	>150	>143
G140S, Q148H	2.17	4.00	>150	>143
E138K,G140S,Q148H	2.42	3.59	>150	>143
G140S,Q148H	2.46	4.73	>150	>143
G140S,Q148H, G163K	2.48	5.68	>150	>143
G140S,Q148H	2.49	5.56	>150	>143
E138K,G140S,Q148H	2.52	5.34	>150	>143
E138K G140S Q148H	2.62	13	>141	>114
G140S,Q148H	2.92	5.46	>150	>143
G140S,Q148R	3.01	6.15	>150	>143
G140S,Q148H	3.81	13	>150	>143
G140S,Q148H	4.37	13	>150	>143
T97A,G140S,Q148H	4.39	15	>150	>143
E138K,G140C,Q148R	5.32	8.58	>150	>143
L74L/M,G140A,Q148R	5.38	8.81	>150	>143
G140S,Q148R	7.05	17	>150	>143
G140S,Q148H,E138A	7.23	16	>150	>143
T97A,G140S,Q148H	7.62	14	>150	>143
L74M,G140C,Q148R	8.36	9.06	>150	>143
E138K,G140A,Q148K	19	6.9	> 56	>143

FC ≤2.5
FC >2.5 & ≤5
FC >5 & ≤10
FC >10

[a] Primary and other integrase strand transfer inhibitor resistance (INSTI-R) mutations are listed. Primary INSTI-R mutations are T66I/A/K, E92Q/G. T97A, Y143C/H/R, S147G, Q148H/K/R, N155H. and other INSTI-R mutations are H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, F121C/Y, A128T, E138A/K, G140A/C/S, P145S, Q146I/K/L/P/R, V151L/A, S153A/F/Y, E157K/Q, G163K/R, E170A, and R263K in IN.

[b] Susceptibility was determined as the fold-change in EC_{50} vs. NL4-3 wild-type vector by Monogram Biosciences, Inc. The biological or lower clinical cut-offs for reduced susceptibility in this assay are 4.0 for DTG, 1.5 for RAL, and 2.5 for EVG. No cut-off has been determined for BIC.

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Results

Table 2. Among 47 HIV-1 Patient-derived Isolates with INSTI Resistance Mutations a Higher Percentage Retained Susceptibility against BIC

INSTI	% of Isolates[a] (Fold-Change vs. WT)			
	(<2.5)	(2.5 – 5)	(5 – 10)	(>10)
BIC	70	15	13	2
DTG	49	17	17	17
EVG	6	2	0	92
RAL	2	4	4	89

[a] The frequency of isolates (%) in each susceptibility stratum is calculated from Table 1.

Results

Table 3. Bictegravir (BIC) Inhibits HIV-1 Clonal Variants from Patients Failing Stribild (EVG/COBI/FTC/TDF) Therapy in Studies GS-US-236-0102 and GS-US-236-0103

Patient ID-Clone#	INSTI Resistance Mutations[a]	Susceptibility (Fold-change vs. WT)[b]			
		BIC	DTG	RAL	EVG
7332-10	None	0.80	0.87	0.79	0.79
7476-5	T66I, E157Q	0.18	0.25	1.63	22
7476-9	T66I, T97A, E157Q	0.26	0.34	2.45	22
6101-12	Q148R	0.74	0.76	32	123
7425-11	E92Q	0.91	1.29	1.95	37
6101-14	N155H	0.98	1.48	6.56	60
6322-1	N155H, G163R	1.03	1.37	16	36
6648-7	E92Q	1.07	1.46	4.20	42
6648-10	E92Q	1.16	1.60	4.20	42
6041-11	E92Q	1.17	1.53	3.67	26
6667-1	E92Q	1.17	1.21	5.09	57
7562-12	N155H	1.19	1.37	13	36
6322-11	N155H	1.20	1.41	11	42
6101-15	E92Q	1.20	1.26	4.41	57
6648-11	E92Q	1.23	1.57	3.97	32
6503-10	E92Q	1.46	1.87	3.88	25
6545-7	N155H	1.51	1.61	16	41
7299-11	Q148R, G140C	1.52	1.97	24	>208

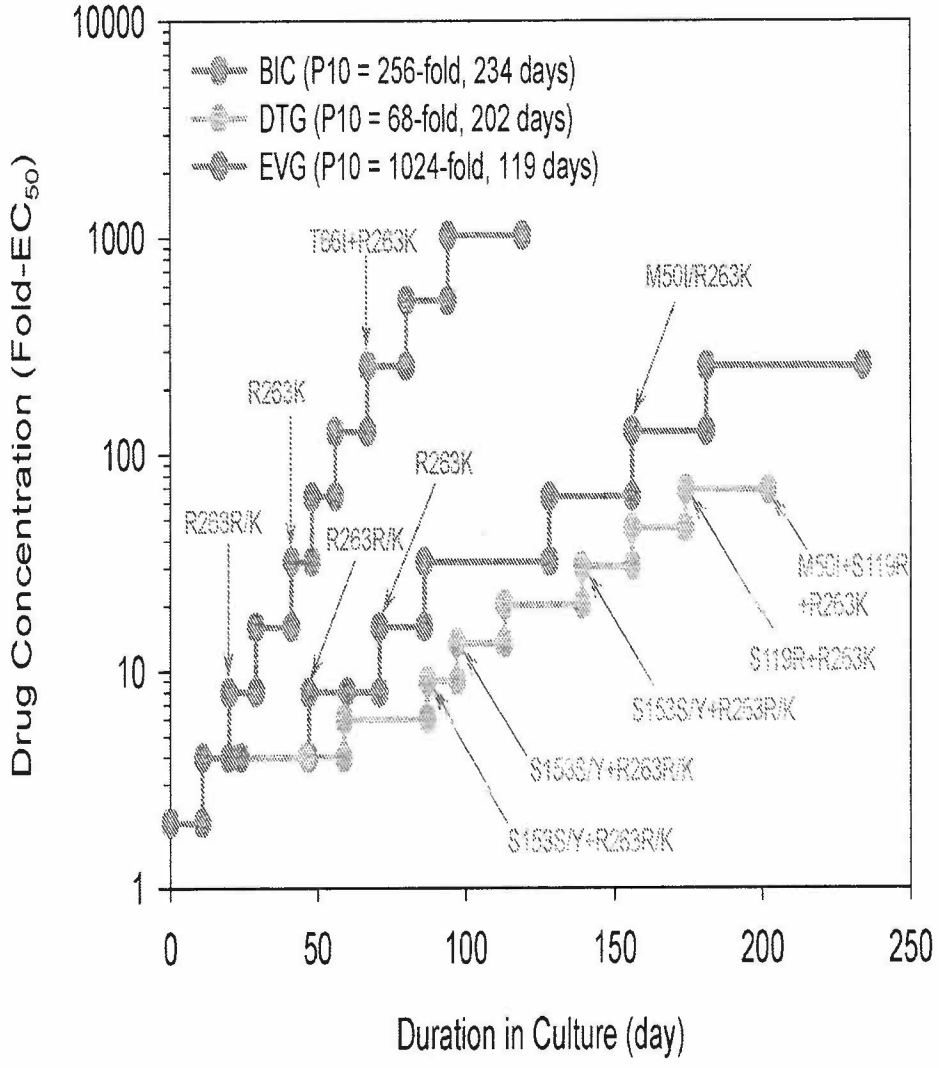
FC ≤ 2.5
FC > 2.5 & ≤ 5
FC > 5 & ≤ 10
FC > 10

[a] Primary and other integrase strand transfer inhibitor resistance (INSTI-R) mutations are listed. Primary INSTI-R mutations are: T66I/A/K, E92Q/G, T97A, Y143C/H/R, S147G, Q148H/K/R, N155H, and other INSTI-R mutations are: H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, F121C/Y, A128T, E138A/K, G140A/C/S, P145S, Q146I/K/L/P/R, V151L/A, S153A/F/Y, E157K/Q, G163K/R, E170A, and R263K in IN.

[b] Susceptibility was determined as the fold-change in EC_{50} values vs. NL4-3 wild-type vector by Monogram Biosciences, Inc. The wild-type virus had a mean EC_{50} of 1.55 nM for BIC. The biological or lower clinical cut-offs for reduced susceptibility in this assay are 4.0 for DTG, 1.5 for RAL, and 2.5 for EVG. No cut-off has been determined for BIC.

Results

Figure 3. Progress of Bictegravir (BIC), DTG and EVG Resistance Selection with HIV-1(IIIb)



9

Results

Table 4. Phenotypic Profile of Selected HIV-1 Passages in the Presence of INSTIs

Selected Virus[a]	Duration of Selection	[Drug] Reached[b]	EC_{50} (nM) (Fold-Resistance Relative to WT)[c]				
	(day)	(nM)	BIC[d]	DTG[d]	EVG[d]	RAL	EFV
HIV-1-IIIb	—	—	2.2 (1)	2.5 (1)	2.1 (1)	8.8 (1)	1.6 (1)
BIC P6	86	24	7.8 (3.5)	8.3 (3.4)	7.8 (3.6)	24.4 (2.8)	1.3 (0.8)
BIC P8	156	96	11.2 (5.0)	12.0 (4.8)	33.6 (15.8)	28.8 (3.3)	1.7 (1.1)
BIC P9	181	192	17.5 (7.9)	19.1 (7.7)	55.0 (25.9)	41.7 (4.7)	2.8 (1.8)
BIC P10	234	384	13.5 (6.1)	14.7 (5.9)	33.0 (15.5)	29.3 (3.3)	2.7 (1.7)
DTG P5	97	14.4	10.6 (4.8)	10.3 (4.2)	9.3 (4.4)	28.0 (3.2)	1.7 (1.0)
DTG P7	139	32.4	21.8 (9.8)	12.4 (5.0)	15.5 (7.3)	39.7 (4.5)	2.3 (1.4)
DTG P9	174	72.9	23.8 (10.7)	15.6 (6.3)	25.1 (11.8)	43.0 (4.9)	2.1 (1.3)
DTG P10	202	109.4	30.0 (13.5)	19.7 (7.9)	69.2 (32.5)	56.9 (6.4)	2.8 (1.8)
EVG P6	56	115	6.8 (3.0)	7.1 (2.8)	48.9 (23.0)	19.9 (2.3)	2.4 (1.5)
EVG P7	67	230	8.9 (4.0)	8.1 (3.2)	203.0 (95.4)	28.7 (3.3)	3.6 (2.2)
EVG P9	94	922	6.8 (3.1)	6.6 (2.6)	295.9 (139.0)	44.9 (5.1)	3.2 (2.0)
EVG P10	119	1843	2.9 (1.3)	3.5 (1.4)	246.4 (115.8)	17.0 (1.9)	2.0 (1.2)

[a] Viral passage numbers are indicated as: P1, P2, P3,...etc.

[b] Resistance selection was initiated at a drug concentration equal to twice the EC_{50} previously determined for each drug (i.e. EC_{50} = 1.5 nM, 1.6 nM and 1.8 nM for BIC, DTG and EVG respectively).

[c] The fold-change is calculated from the ratio of EC_{50} of the selected virus over the EC_{50} of HIV-1 IIIb. The values represent the mean of at least two experiments performed in triplicate.

[d] Maximum observed fold-change for BIC = 7.9-fold, DTG =7.9-fold, EVG = 139-fold (highlighted in red).

Results

Table 5. Phenotypic Profile of Resistance Mutations Selected by BIC

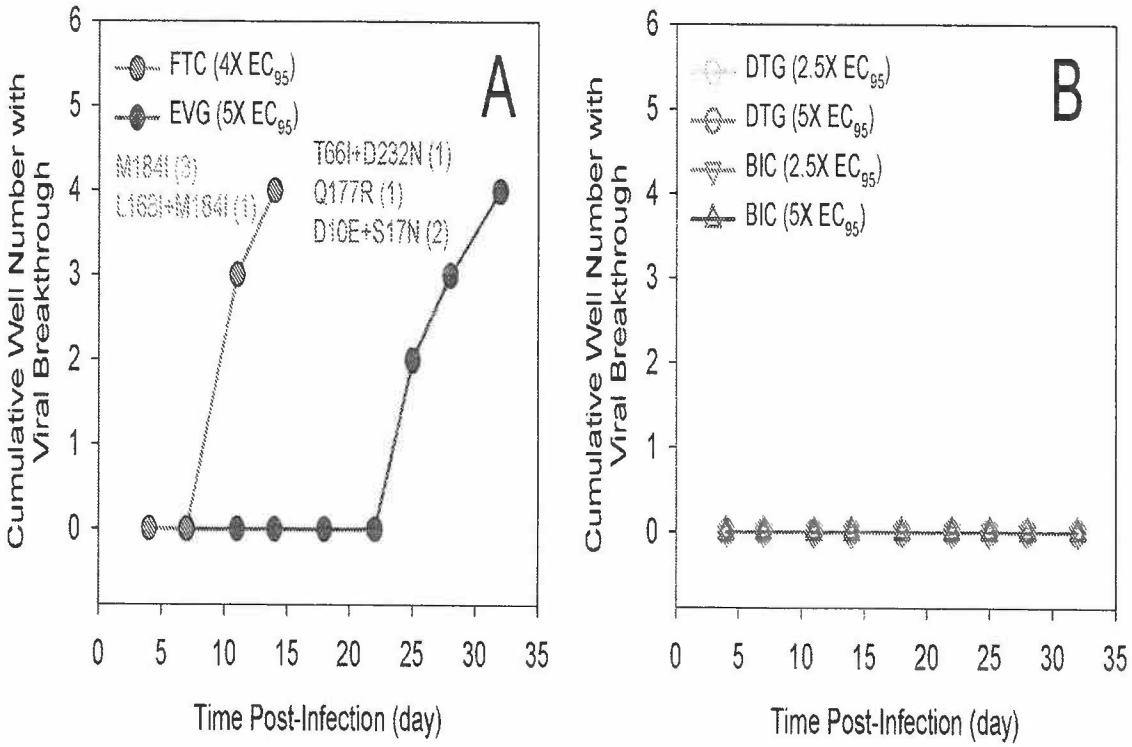
Compound	EC_{50} (nM)[a]	EC_{50} Fold-Change Relative to WT[a]		
	WT[b]	M50I[c]	R263K[c]	M50I/R263K[c]
BIC	1.45 ± 0.20	1.3 ± 0.3	2.2 ± 0.6	2.9 ± 0.8
DTG	1.70 ± 0.07	1.2 ± 0.1	2.1 ± 0.3	2.1 ± 0.3
EVG	1.46 ± 0.36	1.4 ± 0.5	3.8 ± 1.6	5.4 ± 2.7
RAL	6.70 ± 1.93	1.1 ± 0.4	1.2 ± 0.4	1.2 ± 0.5
EFV	0.85 ± 0.46	1.4 ± 0.9	1.2 ± 0.8	1.2 ± 0.7

[a] EC_{50} ± SD and Fold-Change ± SD represent the mean of at least 3 independent determinations in triplicate.
[b] Wild-type virus was generated from HIV-1 DNA clone HXB2.
[c] HIV-1 Integrase (IN) mutant constructed by site-directed mutagenesis on an HXB2 background.

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Results

Figure 4. Bictegravir (BIC) Prevented Resistance Breakthrough of HIV-1 IIIb in MT-2 Cells



- A total of four wells were monitored for resistance breakthrough. The viruses from the breakthrough wells were population sequenced and the mutations detected are shown on the graph with its frequency indicated in parenthesis.
- The concentration of each drug used in breakthrough selection is expressed as a multiple of their antiviral EC_{95}. For DTG and BIC, at 5X EC_{95} the drug concentration is 2- to 3-fold below the tissue culture equivalent C_{min} of the drug defined as the clinical C_{min} adjusted for the absence of human serum protein binding. For EVG, 5X EC_{95} is about equal to the tissue culture equivalent C_{min} whereas for FTC, 4X EC_{95} is ~88-fold the tissue culture equivalent C_{min}.

Results

Table 6. Bictegravir (BIC) Prevented Resistance Breakthrough of HIV-1 BaL in Primary Human CD4+ T-Cells

Drug	Drug Conc. (nM)[a]	p24 Positive Wells[b]	Frequency of Resistant Virus Breakthrough	Drug Resistance Associated Mutations (No. of incidences per 12 or 24 wells)
BIC (C_{min})	138	0/24	0%	No Viral Breakthrough
DTG (C_{min})	73	0/24	0%	No Viral Breakthrough
EVG (C_{min})	48	23/24	54%	T66I (3), E92V (1), E92G (1), Q148R (1), N155H (3), S230R (1), R263K (3), no RAMs (10)
RAL (C_{min})	60	12/12	58%	L74M (1), Q148R (2), N155H (2), G163R (1), G163R+F121Y (1), no RAMs (5)
ATV (C_{min})	300	0/24	0%	No Viral Breakthrough
RPV (C_{min})	8	6/24	25%	V90I+E138K (1), K101E (1), V90I+T240I (1), P225L+F227C (1), M230I (2)
EFV (C_{min})	250	2/12	17%	L100I (2)
FTC ($160 \times EC_{50}$)	1600	14/24	58%	M184I (8), M184V (5), M184T (1)

[a] Tissue culture equivalent C_{min} = clinical C_{min} concentration adjusted for the absence of human serum protein binding.

[b] Viral breakthrough was evaluated in primary CD4+ T-cells after 35 days in culture by p24 ELISA and sequence analysis of p24-positive wells.

Results

Table 7. Bictegravir is Potent Against NRTI-, NNRTI- and PI-Resistant HIV-1 Mutants

Compound	EC_{50} (nM)[a]	EC_{50} Fold-Change[b] Relative to WT											
		NRTI Resistant			NNRTI Resistant					PI Resistant			
	WT	K65R	M184V	6TAMs[c]	K103N	Y181C	Y188L	L100I K103N	K103N Y181C	L10F/ M46I/ I50V	I84V/ L90M	G48V/ I54V/ V82S	G48V/ V82A/ L90M
BIC	1.7 ± 0.5	1.4	1.4	1.4	0.8	1.2	0.9	1.0	1.2	1.9	1.5	1.1	1.3
DTG	1.6 ± 0.5	1.5	1.6	1.5	0.8	1.4	0.9	1.1	1.4	1.4	1.2	1.0	1.0
EVG	2.5 ± 1.5	1.7	1.5	1.2	1.2	1.2	1.3	1.1	1.1	1.4	1.0	0.9	1.0
FTC	385 ± 225	21.5	>300	10.8	–	–	–	–	–	–	–	–	–
TFV	3,716 ± 790	4.6	1.4	7.1	–	–	–	–	–	–	–	–	–
RPV	0.8 ± 0.4	–	–	–	1.5	5.6	24.5	21.9	9.1	–	–	–	–
EFV	1.2 ± 0.4	–	–	–	45.9	3.6	>83	>83	>83	–	–	–	–
DRV	3.5 ± 1.6	–	–	–	–	–	–	–	–	40	3.1	0.4	0.5
ATV	1.6 ± 0.9	–	–	–	–	–	–	–	–	4.9	114	55	30

[a] EC_{50} values (mean ± SD) obtained from three independent experiments performed in triplicate.
[b] Mean EC_{50} fold-changes (mutant/WT EC_{50} ratio) obtained from three independent experiments performed in triplicate.
[c] 6TAMs contains HIV-1 RT mutations M41L, D67N, K70R, L210W, T215Y and K219Q.

2-fold – 10-fold
10-fold – 50-fold
50-fold – 100-fold
> 100-fold

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Conclusions

- Bictegravir (BIC; GS-9883), a novel INSTI, displays an improved resistance profile compared to DTG and markedly improved compared to the first approved INSTIs RAL and EVG against a panel of prospectively defined site-directed HIV integrase mutants.
- Bictegravir had an improved resistance profile compared to EVG, RAL, and DTG in patient isolates, particularly for isolates with high-level INSTI resistance containing combinations of mutations such as E92Q+N155H or G140C/S+Q148R/H/K.
- Clonal HIV-1 isolates from patients with INSTI resistance after Stribild virologic failure retain full susceptibility to bictegravir.
- Bictegravir retains full activity against HIV-1 variants resistant to currently approved antiretrovirals from the NRTI, NNRTI and PI classes.
- *In vitro* resistance selection and breakthrough studies showed that bictegravir displayed a higher barrier to resistance emergence than EVG, and similar to that of DTG.
- Bictegravir selected for HIV-1 variants with low-level resistance (EC_{50} fold-change of 2 to 8) containing the R263K and M50I mutations in the IN coding sequence. The bictegravir-selected variants exhibit low level cross-resistance to RAL and DTG, and intermediate cross-resistance to EVG, but remain susceptible to other classes of antiretrovirals.
- In summary, bictegravir exhibits an unsurpassed resistance profile that supports its further clinical development for the first-line treatment of HIV infection. In addition, bictegravir may be suitable for the once-daily treatment of HIV-infected patients with preexisting INSTI resistance.

Discovery of Bictegravir (GS-9883), a Novel, Unboosted, Once-Daily HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Improved Pharmacokinetics and *In Vitro* Resistance Profile

Scott E. Lazerwith, Ruby Cai, Xiaowu Chen, Greg Chin, Manoj C. Desai, Sara Eng, Reginald Jacques, Mingzhe Ji, Greg Jones, Hal Martin, Carrie McMahon, Michael Mish, Philip Morganelli, Judy Mwangi, Hyung -Jung Pyun, Uli Schmitz, George Stepan, Javier Szwarcberg, Jennifer Tang, Manuel Tsiang, Jianhong Wang, Kelly Wang, Kirsten White, Lauren Wiser, Julia Zack, Haolun Jin

ASM Microbe
June 2016
Boston, MA
Poster #414

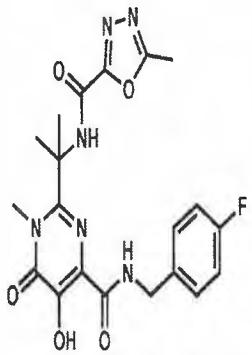
Introduction

Currently approved integrase strand-transfer inhibitor (INSTI) based treatments comprise 5 of 6 DHHS recommended regimens for HIV-1 infection.[1] Limitations of early INSTIs include twice-daily dosing (raltegravir, RAL) and the need for a pharmacokinetic enhancer (elvitegravir, EVG). Dolutegravir (DTG) is a more recently-approved INSTI that exhibits an improved resistance profile compared to RAL and EVG, and is dosed once-daily in most naïve patients.[2] Limitations of DTG include the need for twice-daily dosing for integrase experienced patients due to non-linear pharmacokinetics when dosing >50 mg once-daily,[2] as well as reduced susceptibility to many integrase double and triple mutants.[3] In addition, DTG shows moderate activation of PXR, raising the risk of DDIs with other agents,[4] and modest increases in patients' serum creatinine, likely due to inhibition of OCT-2.[5]

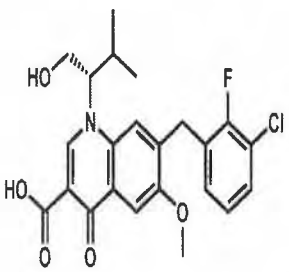
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3. See (a) Tsiang, M., et al. ASM Microbe 2016. Poster #416. and (b) White, K.; Cihlar, T.; Miller, M. D. 14th European Workshop on HIV & Hepatitis, 2016. Abstract O-01.
4. Chu, V.; Einolf, H. J.; Evers, R.; Kumar, G.; Moore, D.; Ripp, S.; Silva, J.; Sinha, V.; Sinz, M.; Skerjanec, A. Drug Metabolism and Disposition, 2009, 37, 1339-1354.
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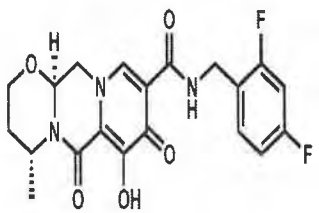
Figure 1. Structures of Currently Approved INSTIs



1
RAL



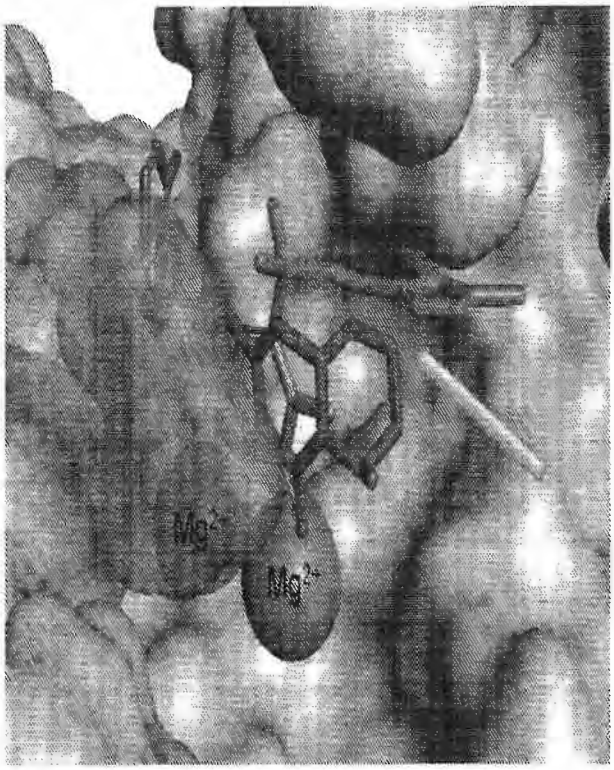
2
EVG

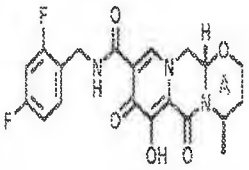


3
DTG

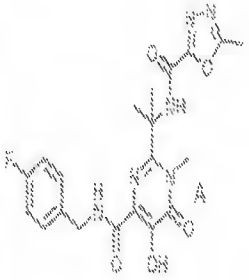
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Figure 2. INSTIs Bind at the Integrase-vDNA Interface[6]





3, DTG
small, flat A-ring



1, RAL
no A-ring

- Little binding to hydrophobic surface near the A-ring of INSTIs (green arrow).
- Hypothesis: Larger, three-dimensional A-rings may improve INSTI potency.

6. Figure made by the overlay of DTG and RAL bound in the active site of prototype foamy virus (PFV) described in: Hare, S., et al. Mol Pharmacol. 2011, 80, 565-572.

Methods

- Antiviral potency and cytotoxicity were assessed in MT-4 and MT-2 T-cell lines.
- Metabolic stability with pooled hepatic microsomal fractions was determined using the in vitro half-life method. Cofactors were NADPH (as a regenerating system) and UDP-glucuronic acid. Incubations were at 37°C and disappearance of substrate was monitored by sequential removal of aliquots over 60 min followed by analysis by LC-MS/MS. In vitro half- life values were determined and then scaled to predicted hepatic metabolic clearance using the well-stirred liver model.
- Protein binding was determined by equilibrium dialysis with a Dianorm device (Harvard Apparatus, Holliston MA) with a semipermeable membrane (10 kDa cut-off) separating two 1 mL PTFE half-cells.[7] For free fraction studies, dialysis was against isotonic phosphate buffer.
- Kinetic solubility studies were carried out by adding compound dissolved in DMSO to phosphate-buffered saline (pH 7.4) to a target concentration of 100 μM (final DMSO concentration 1.0%). After shaking for 1 hr, non-dissolved material was removed by centrifugation and the equilibrium concentration remaining in the supernatant determined by LC-UV analysis.
- Thermodynamic solubility studies were carried out by adding compound (1 mg) to aqueous media (1 mL). This mixture was sonicated briefly and stirred for a minimum of 12 hours. The suspension was centrifuged and the supernatant was analyzed by UPLC.

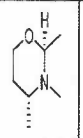
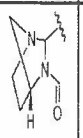
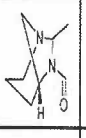
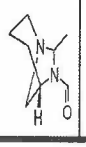
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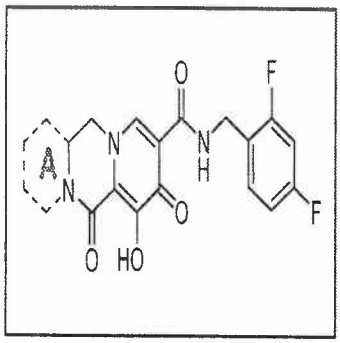
Methods, cont'

- Activation of PXR was assessed via a reporter gene assay in a stably transformed tumor cell line (DPX2) at six concentrations. %Emax is determined relative to 10 μM rifampicin
- Animal PK: test compounds were dosed in rats or dogs via 30-min IV infusion or oral administration. Serial blood samples were collected and LC/MS/MS methods were used to measure the concentrations of test compounds in plasma. Non-compartmental pharmacokinetic analysis was performed on the plasma concentration-time data to generate the PK parameters.

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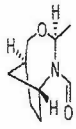
Table 1. SAR of the A-ring: Diaza-Bridging Bicycles

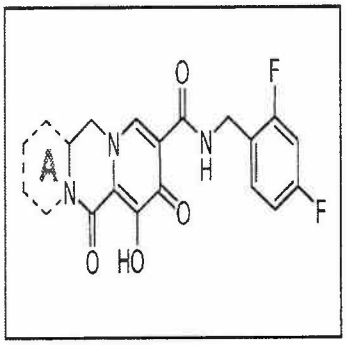
	A Ring	EC_{50} (nM)	Human MS $t_{1/2}$, (min)	%free (human plasma)	PXR (%Emax, 15μM)	G140S/ Q148R fold shift
3 (DTG)		2.0	>395	0.7	51	4.8
4		14.8	202	21	3	–
5		5.3	278	1.8	0	11
6		3.3	>395	20	2	599
7		2.8	212	3.0	2	24



- Bicyclic diaza A-rings did not provide potency increase.
- Bicyclic diaza A-rings show markedly lower PXR activation compared with monocyclic **3**.
- Microsomal stability and G140S/Q148R potency is often compromised.
- Free fraction in human plasma higher than desired.

Table 2. SAR of the A-ring: Oxaza-Bridging Bicycles

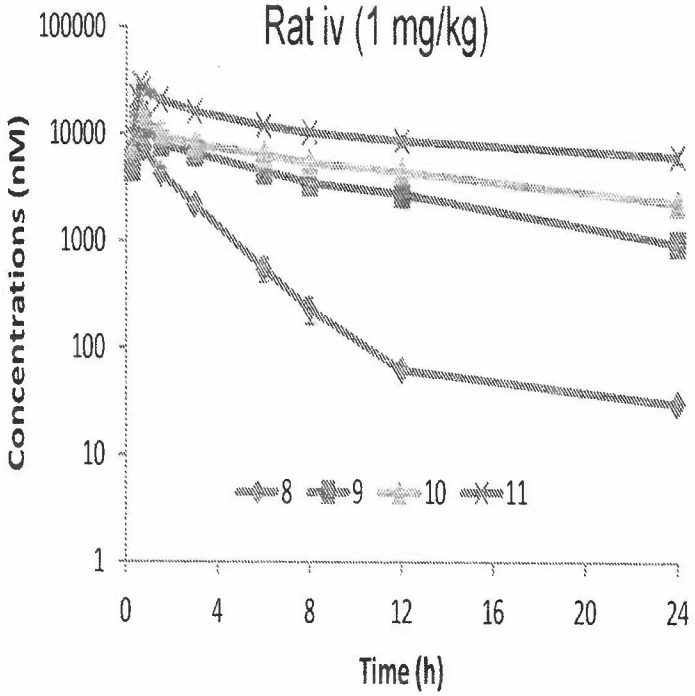
	A Ring	EC_{50} (nM)	Human MS $t_{1/2}$, (min)	%free (human plasma)	PXR (%Emax, 15μM)	G140S/ Q148R fold shift
3 (DTG)		1.7	>395	0.7	51	4.8
8		3.5	>395	5.8	7	4.5
9		2.5	>395	4.7	7	3.2
10		2.0	>395	0.75	8	18.2
11		2.2	>395	0.28	5	3.4
12		2.3	>395	1.3	7	1.3



- Bicyclic oxaza A-rings maintain but do not improve potency compared with monocyclic **3**.
- Bicyclic oxaza A-rings also show much lower PXR activation than monocycle **3**.
- High metabolic stability is seen in all bicyclic oxaza A-rings.
- [3.2.1] bicyclic A-rings **10** and **11** display favorably low levels of free fraction in human plasma.

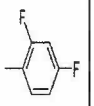
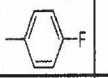
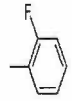
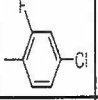
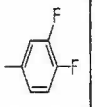
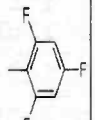
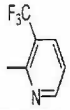
Table 3. Rat PK of Bicyclic A-Ring Analogs Show Higher Protein Binding Leading to Longer Mean Residence Times

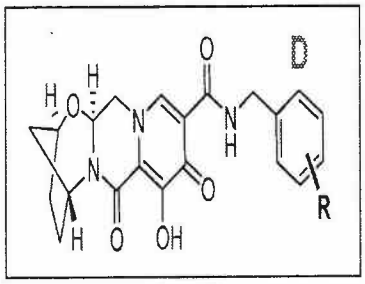
	MS (rat) $t_{1/2}$ (min)	%free (rat plasma)	Mean Residence Time (rat)
8	395	0.32	3 h
9	395	0.06	11 h
10	395	0.03	18 h
11	395	0.016	30 h



- For stable and highly protein bound compounds, mean residence times in rat correlate strongly with plasma protein binding.

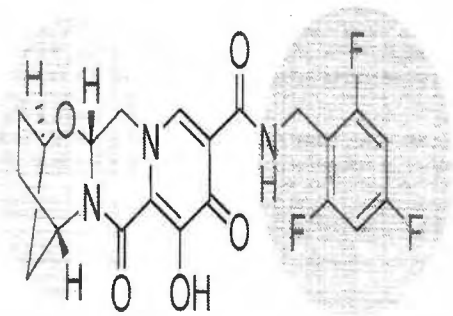
Table 4. SAR Study Suggests Advantages of 2,4,6-Trifluorophenyl as the D-ring substituent

	D Ring	EC_{50} (nM)	Human MS $t_{1/2}$, (min)	%free (human plasma)	Solubility (pH 1 / 7)	G140S/ Q148R fold shift
10		2.0	395	0.7	34 / 53	18
13		1.9	379	4.8	6 / 4	–
14		1.8	221	2.9	21 / 22	–
15		2.0	175	1.2	16 / 12	44
16		4.0	314	1.3	92 / 81	67
17		2.2	395	1.6	87 / 85	8
18		33	–	–	–	–



- Using A-ring **10**, a study of D-ring substituents was performed.
- Most analogs showed reduced metabolic stability.
- 2,4,6-trifluorophenyl analog **17**, shows improved solubility and higher potency against G140S/Q148R mutant compared with difluorophenyl analog **10**.

Figure 2. Simultaneous incorporation of Novel A- and D-rings Gives Bictegravir



Bictegravir (GS-9883)

wt EC_{50} = 1.9 nM

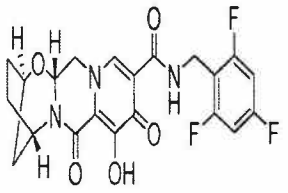
G140S/Q148R

fold-shift = 2.0

11

Table 5. In Vitro Profile of Bictegravir Compared with RAL, EVG and DTG

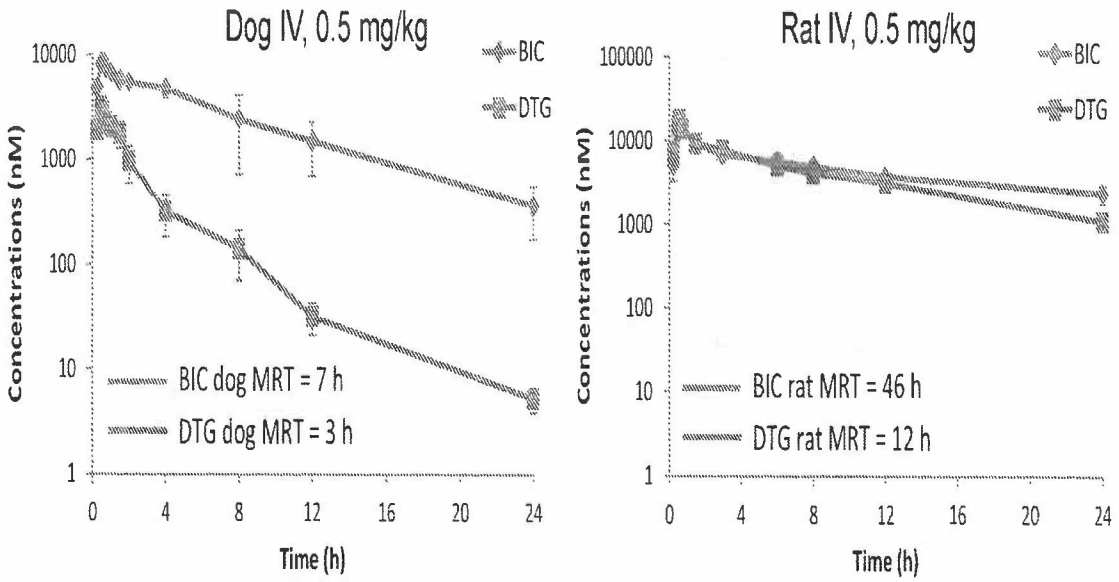
	RAL	EVG	DTG	BIC
EC_{50} (nM, MT4)	8.9	1.8	1.7	1.9
Plasma Adjusted EC_{50} (nM, MT4)	21	43	47	83
human liver microsomal Cl (L/h/kg)	0.24	0.43	0.16	0.17
%free human plasma	12.2	0.5	0.7	0.30
OCT-2 IC_{50} (μM)			0.13	0.49
PXR %Emax@ 15μM			51	18
Thermodynamic Solubility (pH = 7, μg/mL)	1906	2	53	119
G140S/Q148R fold shift	249	297	4.8	2.0



Bictegravir

- BIC shows improved G140S/Q148R potency compared to previous agents.
- BIC shows reduced OCT-2 inhibition, reduced PXR activation, and higher solubility compared with DTG.
- BIC shows low human microsomal clearance, high plasma protein binding and was predicted to have a long human $t_{1/2}$.

Figure 3. Bictegravir Exhibits an Excellent Preclinical PK Profile



Species	Formulation (dose)	3 (DTG)	BIC
%F rat	Solution (0.5 mg/kg)	52	50
%F dog	Suspension (1 mg/kg)	17	28

- Bictegravir shows longer half-lives in intravenous PK studies and higher exposure from solid oral dosing studies than DTG in pre-clinical species

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Conclusions

- To discover higher potency INSTIs, a series of oxo-pyridones with larger, three-dimensional A-rings were synthesized.
- SAR studies of these A-ring analogs led to the discovery of bicyclic A-ring systems which showed very low PXR activation, and specific [3.2.1] oxaza A-rings that showed high protein binding and long mean residence times in animals.
- SAR studies of the D-ring resulted in the 2,4,6-trifluorophenyl group, which improved solubility and resistance profile.
- Simultaneous incorporation of novel A- and D-rings gives bictegravir (BIC, GS-9883).
- BIC shows high potency against wild-type HIV-1and improved potency against many integrase resistant mutants compared with EVG, RAL and DTG.[3]
- BIC shows longer mean residence times in both rat and dog compared with DTG.
- BIC exhibits reduced in vitro PXR activation and lower OCT-2 inhibition compared with DTG.
- In human POC study, BIC has an average human $t_{1/2}$ of approximately 19 h, confirming once-daily dosing potential.[8]
- In summary, an extensive SAR study led to the discovery of bictegravir, a novel, potent, once-daily, INSTI with an improved resistance profile. BIC is currently being studied in clinical trials as a single tablet regimen combination with FTC and TAF.

8. Gallant, J. et al. ASM Microbe 2016, Poster #415.

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Antiviral Activity of Bictegravir (GS-9883), a Potent Next Generation HIV-1 Integrase Strand Transfer Inhibitor

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Gilead Sciences, Foster City, CA

ASM Microbe
June 2016
Boston, MA
Poster #416

Introduction

- Integrase strand transfer inhibitors (INSTIs) are a class of antiretroviral drugs for the treatment of HIV-1 infection and inhibit HIV-1 replication by blocking the strand transfer step of viral DNA integration into the host genome.

- The first two INSTIs, raltegravir (RAL) dosed twice-daily and elvitegravir (EVG) dosed-once daily with boosting, are approved for clinical use as components of combination therapy. However, RAL and EVG have overlapping resistance profiles such that viruses resistant to one drug are cross-resistant to the other drug, which ultimately precludes the sequential use of these two INSTIs.

- Dolutegravir (DTG) is also an INSTI and is dosed once-daily without boosting and exhibits a higher barrier to resistance development. However, due to limited absorption above 50 mg, twice-daily dosing is required in patients with past INSTI use, with INSTI resistance, or suspected INSTI resistance. Twice-daily dosing is also required when co-administered with cytochrome P450 (CYP) and/or uridine diphosphate glucuronosyl-transferase (UGT) inducers.

- Our goal was to develop a novel INSTI with once-daily dosing potential, improved tolerability, and high efficacy against INSTI-associated resistance.

- Bictegravir (BIC; GS-9883) is a novel potent once-daily unboosted INSTI currently in clinical development in combination with tenofovir alafenamide (TAF) and emtricitabine (FTC) in a single tablet regimen for the treatment of HIV-1 infection. In this study, we report the virologic characterization of BIC.

Methods

- The enzymatic inhibitory activity of BIC (GS-9883) was tested against purified wild-type HIV-1 integrase enzyme using homogeneous time-resolved FRET-based 3'-processing and strand transfer assays.
- Antiviral potency and cytotoxicity were assessed in MT-2 and MT-4 T-cell lines and primary human CD4+ T-cells and macrophages.
- Inhibition of chromosomal HIV-1 integration was assessed by qPCR of 2-LTR circles and integration junctions in MT-2 cells infected with HIV-1 (IIIb).
- A panel of 14 HIV-1 and one HIV-2 clinical isolates from the collection of Southern Research Institute was used for antiviral profiling in a PBMC-based antiviral assay using the quantitative reverse transcriptase endpoint activity through contract service with the Southern Research Institute (Frederick, MD).
- Antiviral activity of BIC was also tested against several non-HIV viruses.
- Cytotoxicity of BIC was tested in four non-target cell lines (Huh-7, HepG2, PC-3, MRC-5) and human primary hepatocytes.
- Antiviral activity of BIC in pairwise combination with other antiretrovirals was assessed. The data were analyzed for the effect of pairwise combination using MacSynergy™ II software.

Results

Table 1. Bictegravir (BIC) Exhibits Potent Antiretroviral Activity in Human T-cell lines

Compound	MT-2 Cells[a]			MT-4 Cells						
	EC_{50} (nM)	CC_{50} (nM)	Selectivity	EC_{50} (nM)[b]	CC_{50} (nM)[a]	Selectivity	Hill Slope[b]	EC_{95} (nM)[e]	EQDS Shift[d] (Fold-change)[c]	$PAEC_{95}$[f] (nM)
BIC	1.5 ± 0.2	10,300 ± 2500	6,867	1.9 ± 0.6	3,700 ± 93	1,926	2.1 ± 0.3	8.3	43.6 ± 7.7	361
DTG	1.5 ± 0.2	5,350 ± 200	3,567	1.7 ± 0.2	15,000 ± 1900	8,634	2.0 ± 0.3	7.4	27.5	204

[a] EC_{50} and CC_{50} values represent the mean ± SD of at least 4 independent determinations in triplicate. Test compounds were 3-fold serially diluted.

[b] EC_{50} values and Hill slopes represent the mean ± SD of 8 independent determinations in quadruplicate. Test compounds were 1.24-fold serially diluted.

[c] Values represent mean ± SD of 3 independent determinations for BIC and mean of two independent determinations for DTG.

[d] Protein shift based on equilibrium dialysis (EQDS) of compound between culture medium and human serum.

[e] EC_{95} is calculated from EC_{50} and Hill slope, n, using the equation: $EC_{95} = EC_{50} \times (95/5)^{(1/n)}$

[f] $PAEC_{95}$ = protein adjusted EC_{95}.

Results

Table 2. Antiretroviral Activity of Bictegravir (BIC) in Human Primary T-Cells and Macrophages

Compound	Human CD4+ T-Lymphocytes[a]			Human Macrophages[a]		
	EC_{50} (nM)	CC_{50} (nM)	Selectivity	EC_{50} (nM)	CC_{50} (nM)	Selectivity
BIC	1.5 ± 0.3	13,000 ± 4,000	8,700	6.6 ± 4.1	29,800 ± 7,700	4,500
DTG	1.0 ± 0.3	52,000 ± 8,500	52,000	3.1 ± 2.5	24,900 ± 1,200	8,000

[a] EC_{50} and CC_{50} values represent the mean ± SD of triplicate measurements in four independent donors.

Results

Table 3. Antiretroviral Activity of Bictegravir (BIC) against Diverse Clinical Isolates of HIV

HIV-1 Subtype	HIV-1 Isolate	Genbank Accession #	EC_{50} (nM)[a]		
			BIC[b]	DTG[c]	AZT
A	92RW016	AF009409	0.74	0.35	2.61
A	92UG037	AB253428	1.71	0.93	10.9
B	Ba-L	AY713409	0.35	0.29	3.39
B	89BZ_167	AY173956	0.88	1.13	2.65
B	91US001	AY173952	0.87	0.84	5.61
B	91US004	AY173955	0.82	0.94	2.74
C	93IN905	AF067158	0.15	0.15	1.61
C	98US_MSC5016	AY444801	1.4	0.92	10.3
D	98UG_57128	AF484502	0.31	0.67	0.55
D	99UG_A07412M1	AF484477	1.06	0.93	9.99
E	96TH_M02138	AY713424	0.8	0.69	5.79
E	96TH_NI1046	AY713421	0.28	0.3	2.6
F	93BR020	AF005494	1.13	0.37	8.72
G	01CM1475MV	AY371138	< 0.05	0.09	0.98
HIV-2	CDC 310319	AY965902	1.11	2.13	4.1

[a] EC_{50} values represent the mean of triplicate measurements in human PBMCs.
[b] BIC EC_{50} range: <0.05 - 1.71 nM against HIV-1.
[c] DTG EC_{50} range: 0.09 - 1.13 nM against HIV-1.

Results

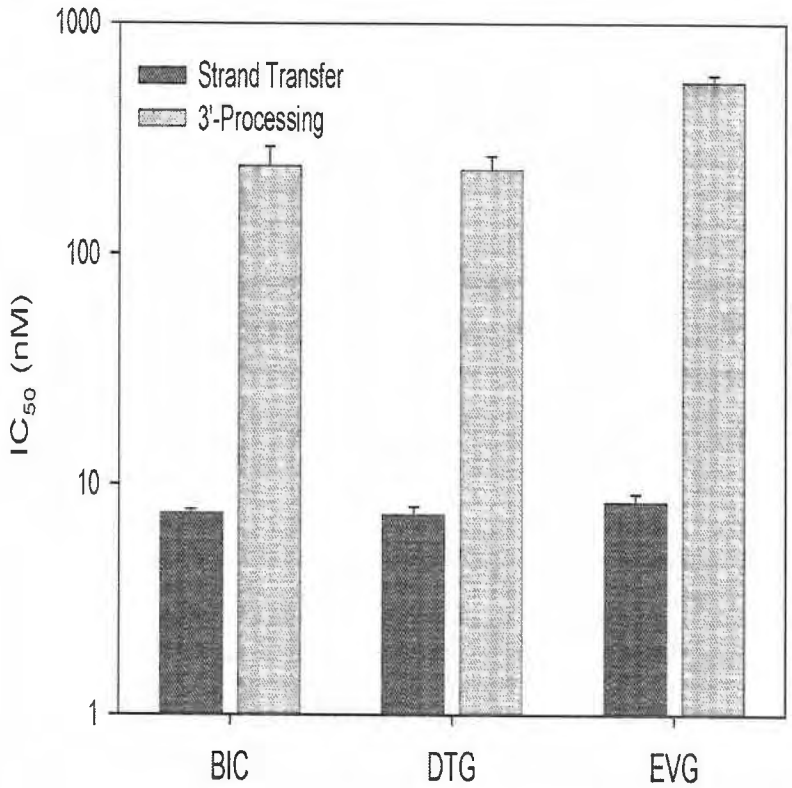
Table 4. Bictegravir (BIC) is not Cytotoxic in Non-Target Cell Lines and Primary Hepatocytes

Compound	CC_{50} in Cell Lines (μM)[a]				CC_{50} in Primary Human Hepatocytes (μM)[b]	
	Huh7	HepG2	PC3	MRC5	Donor 1	Donor 2
	Human hepatoma	Human hepatoma	Human prostate cancer	Normal human fibroblasts		
BIC	43.6	34.6	> 44	> 44	>100	>100
DTG	> 44	43.3	> 44	30.7	>100	>100
Puromycin	0.72	1.68	0.62	0.36	1.2	0.83

[a] CC_{50} values represent the mean of three independent runs in triplicates.
[b] CC_{50} values were obtained from 2 donors with each assay performed in duplicate.

Results

Figure 1. Bictegravir (BIC) is a Strand Transfer Inhibitor of HIV-1 Integrase



IC_{50} (nM)[a]	BIC	DTG	EVG
Strand Transfer	7.5 ± 0.3	7.4 ± 0.6	8.4 ± 0.7
3'-Processing	241 ± 51	232 ± 33	556 ± 40

[a] The data represent the mean ± SD of 3 independent experiments performed in triplicates.

Results

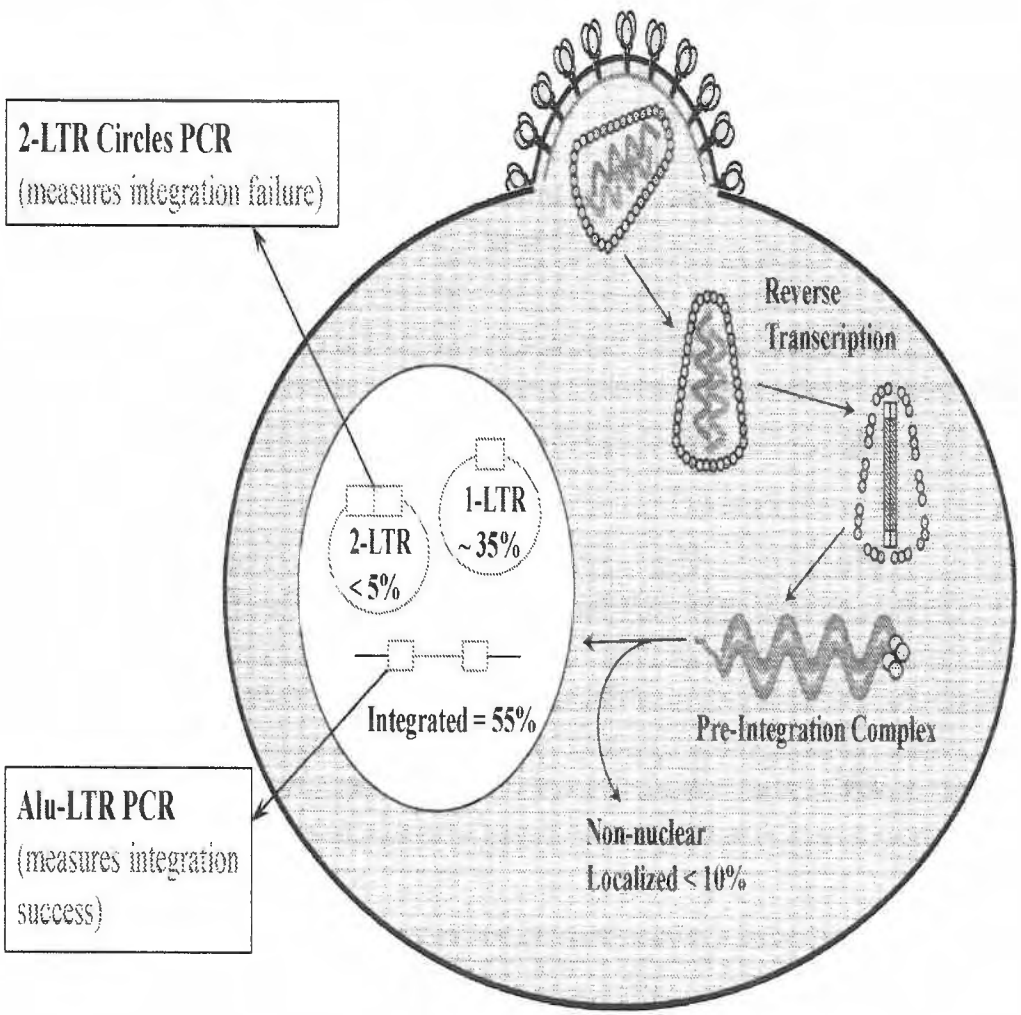
Table 5. Bictegravir (BIC) is an Authentic Inhibitor of HIV-1 Integration in HIV-1 (IIIb) Infected MT-2 Cells

Compound	Drug Concentration (nM)[a]	Integration Failure	Assessment of Direct Effect on Integration	
		2-LTR Circles (fold-change)[b]	Late-RT (fold-change)[b]	Alu-LTR (fold-change)[b]
DMSO	—	1	1	1
BIC	28	3.3	0.9	0.01
DTG	31	4.5	0.8	0.02
EFV[c]	17	0.1	0.2	0.08
DRV[c]	57	1.1	0.9	0.8

[a] Compounds were applied to HIV-1 (IIIb) infected MT-2 cultures at ~20-fold their respective antiviral EC_{50} value.
[b] The quantitative PCR data of HIV target sequences were normalized against the corresponding quantitative PCR data for the globin gene from the same sample and represent the mean of two independent experiments. For 2-LTR circles PCR and Alu-LTR PCR, refer to Figure 2. Fold-change is relative to the DMSO control.
[c] EFV = efavirenz (an HIV reverse transcriptase inhibitor), DRV = darunavir (an HIV protease inhibitor).

Results

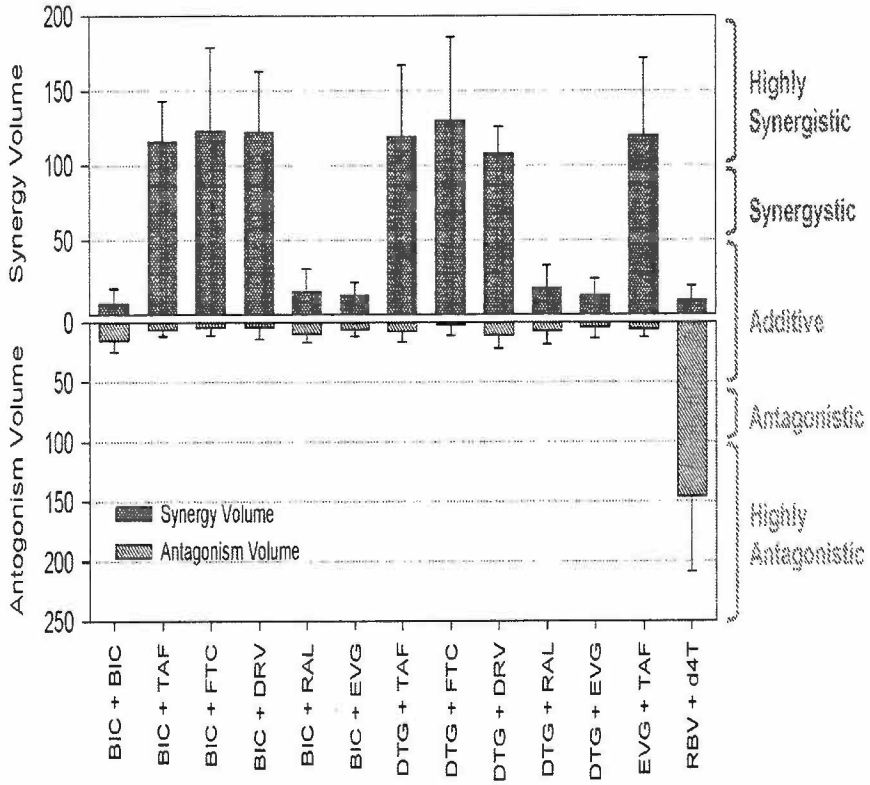
Figure 2. Distribution of HIV-1 DNA Species in an Infected Cell



Adapted from Zennou et al., 2000, Cell 101:173-185

Results

Figure 3. Bictegravir (BIC) is Synergistic with TAF, FTC, and DRV



[a] EVG = elvitegravir, RBV = ribavirin, d4T = stavudine, DTG = dolutegravir, TAF = tenofovir alafenamide, FTC = emtricitabine, DRV = darunavir.

[b] The effect of pairwise drug combination was analyzed by the MacSynergy™ II software. The results were expressed as the mean synergy/antagonism volumes (nM^2.%) calculated at the 95% confidence interval from at least 3 independent experiments done in triplicates.

Conclusions

- Bictegravir is a novel specific inhibitor of HIV-1 integrase strand transfer activity and an authentic inhibitor of integration in HIV-1 infected target cells.
- Bictegravir is a potent and selective inhibitor of HIV-1 replication in lymphoblastoid T-cell lines, primary human CD4+T cells, and macrophages with EC_{50} values ranging from 1.5 to 6.6 nM and selectivity indices ranging from 1,926 to 8,700.
- Bictegravir is active against diverse subtypes of wild-type HIV-1 clinical isolates and HIV-2 with a mean EC_{50} of 0.75 nM and a range of 0.05 – 1.71 nM.
- The protein adjusted EC_{95} of bictegravir is 361 nM, with a steady-state clinical trough-concentration of 6.9 µM and an IQ of ~19 in human subjects administered 75 mg once daily under fasted conditions.
- Bictegravir has low cytotoxicity in multiple non-target human cell lines and in primary human hepatocytes.
- Bictegravir is a specific inhibitor of HIV, with no measurable antiviral activity against non-HIV viruses, including HBV, HCV, Influenza A and B, HRV and RSV (data not shown).
- Bictegravir exhibited synergistic *in vitro* antiviral effects when combined with antiretrovirals from other classes, including TAF, FTC, and DRV.
- In conclusion, this virologic profile supports further clinical development of bictegravir as a novel potent once-daily unboosted integrase strand transfer inhibitor in a single tablet regimen combination with FTC and TAF.

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Divalent metals and pH alter raltegravir disposition *in vitro*.

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Key words: Raltegravir, HIV, HAART, pharmacokinetics, integrase inhibitors, permeability, P-gp, ABC transporters, pH, metal binding

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Abstract

Introduction: Raltegravir shows marked patient pharmacokinetic variability with gastrointestinal pH and divalent metal binding being potential factors. We have investigated raltegravir solubility, lipophilicity, pKa and permeability *in vitro* to elucidate known interactions with omeprazole, antacids, and food, all of which increase gastric pH.

Methods: Solubility of raltegravir was determined at pH 1 to 8. Lipophilicity of raltegravir was determined using octanol/water partition. Raltegravir pKa was determined using UV spectroscopy. The effects of pH, metal salts and omeprazole on raltegravir cellular permeability were determined using Caco-2 monolayers. Cellular accumulation studies were used to determine the interplay between pH and ABCB1 transport on raltegravir accumulation. Samples were analysed using LC-MS/MS or scintillation counting.

Results: Raltegravir at 10 mM was partly insoluble at pH6.6 and below. Raltegravir lipophilicity is pH-dependent and reduced as pH was increased from 5 to 9. The pKa of raltegravir was 6.7. Raltegravir cellular permeability was heavily influenced by changes in extracellular pH, where apical-to-basolateral permeability reduced 9-fold ($p<0.05$) when apical pH was increased from 5 to 8.5. Raltegravir cellular permeability was also reduced in the presence of magnesium and calcium. Omeprazole did not alter raltegravir cellular permeability. Cellular accumulation of raltegravir was increased independently by inhibiting ABCB1 and by lowering extracellular pH from pH 8 to 5.

Discussion: Gastrointestinal pH and polyvalent metals can potentially alter the pharmacokinetic properties of raltegravir and these data provide a rationale for the

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variability in raltegravir exposure in patients. The evaluation of how divalent metal-containing products, such as multivitamins that do not affect gastric pH, alter raltegravir pharmacokinetics in patients is now justified.

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Introduction

Raltegravir, the first licensed integrase inhibitor for treatment of HIV, has potent *in vitro* and clinical activity (22). The primary route of raltegravir metabolism is glucuronidation via UDP glucuronosyltransferase 1A1 (14) and the drug is not a substrate or inhibitor of the major cytochrome P450 enzymes (12). However, there are known drug interactions involving UGT1A1 which may alter raltegravir plasma exposure. Atazanavir inhibits UGT1A1, causing an increase in raltegravir exposure (4) and rifampicin mediates induction of UGT1A1 causing a decrease in raltegravir exposure (27). In addition, raltegravir is a weak substrate for the drug transporters ABCB1, SLC22A6 and SLC15A1 and also inhibits SLC22A6 *in vitro* (18). Marked inter- and intra-patient variability in raltegravir plasma exposure exists and the relationship between the pharmacokinetics (PK) and pharmacodynamics (PD) of the drug remains poorly understood (7).

The pH of the gastrointestinal (GI) tract is an important factor in the absorption of many drugs, potentially altering drug release, solubility, chemical stability, charge state and/or intestinal permeability (5). Ionic drugs with a pKa within the physiological pH range are susceptible to alterations in GI pH because drugs with an ionic charge are less able to permeate the intestine wall without active transport. In healthy volunteers, raltegravir area under the curve (AUC), maximum plasma concentration (C_{max}) and plasma concentration twelve hours after dosing (C_{12hr}) increased 3.1, 4.2 and 1.5-fold, respectively, following five days of 20mg once daily omeprazole (13); higher solubility at increasing pH was postulated as the mechanism of interaction (2). However, GI pH was not directly measured in this study and there are no published data showing the effect of pH on raltegravir solubility *in vitro*. In a similar study using

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106 HIV-infected patients, raltegravir geometric mean ratio (GMR) for AUC, C_{max} and
107 C_{12hr} was 1.4, 1.5 and 1.2-fold higher, respectively, following five days of 20mg once
108 daily omeprazole and 1.5, 1.6 and 1.1-fold higher, respectively, following a single
109 dose of 20mg famotidine (24). HIV-infected patients, particularly those with
110 advanced disease progression, have higher gastric pH than uninfected individuals
111 (25) and this may explain why acid-reducing agents showed less impact on
112 raltegravir PK in HIV-infected patients in the study by Rhame *et al* (24).
113
114 After ingestion of a meal, gastric pH is briefly elevated due to the buffering and
115 diluting effect of the food (5). The extent of gastric pH increase and the rate at which
116 pH is lowered to fasting state levels depends on the volume of the food, the ability of
117 the food to stimulate gastric acid secretion and the rate of gastric emptying. Other
118 factors, such as fat and protein content of food, are also important. In a steady-state
119 food-effect study using healthy subjects, alterations in raltegravir exposure from a
120 fasted state were shown for low fat (GMR of AUC, C_{max} and C_{12hr} of 0.54, 0.48 and
121 0.86, respectively), medium fat (GMR of AUC, C_{max} and C_{12hr} of 1.13, 1.05 and 1.66,
122 respectively) and high fat (GMR of AUC, C_{max} and C_{12hr} of 2.11, 1.96 and 4.13,
123 respectively) meals (1). However, this study concluded that the effect of food was not
124 clinically significant and recommended that raltegravir can be taken without regard to
125 food.
126
127 Integrase strand transfer inhibitors work by chelating magnesium ions at the
128 integrase enzyme active site, therefore preventing the insertion of viral DNA into the
129 host cell's DNA (8). Therefore, binding with free magnesium (and possibly other
130 polyvalent cationic metals) in the GI tract is likely to alter raltegravir absorption.

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Indeed, interactions between integrase inhibitors and metal-containing products have been investigated. Raltegravir C_{12hr} and T_{max} were reduced by 67% and 1.75 hours, respectively, when taken with an antacid containing magnesium and aluminium, although the AUC and C_{max} were not significantly altered (15). Importantly, 75% of subjects taking antacids had a raltegravir C_{12hr} lower than 15 ng/mL (IC_{95} of raltegravir in 50% human serum). We hypothesised that this interaction may be mediated by an increase in raltegravir solubility with increased pH (decreasing the T_{max}) and binding of raltegravir to the metal ions in the antacid (decreasing C_{12hr}).

This study aimed to establish *in vitro* the solubility, lipophilicity and pKa of raltegravir using a range of buffered pH solutions and solvents. The impact of pH, metal cations and omeprazole on raltegravir transcellular permeability across an *in vitro* model of absorption were also determined. Raltegravir is a substrate of ABCB1 *in vitro* (18) and the interplay between pH and ABCB1 transport was investigated in cellular accumulation assays to ascertain whether active transport of raltegravir by ABCB1 was influenced by pH.

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148 **Methods**

149

150 **Chemical reagents and materials**

151 Caco-2 cells were purchased from the European Collection of Cell Cultures
152 (Salisbury, UK). Raltegravir potassium salt and [^{3}H] raltegravir were gifts from Merck
153 (New Jersey, USA). Lopinavir was a gift from Abbott (Illinois, USA). [^{3}H] lopinavir
154 was purchased from Moravek Biochemicals (California, USA). Tariquidar was
155 purchased from Xenova (Sloane, UK). Acetonitrile was purchased from J. T Baker
156 (Deventer, Holland). [^{14}C]mannitol was purchased from American Radiolabelled
157 Chemicals (Missouri, USA). All other reagents were obtained from Sigma (Poole,
158 UK).

159

160 **Creation of buffered pH solutions for solubility, lipophilicity and pKa**
161 **experiments**

162 Stock aqueous solutions were buffered to pH 1 (50 mM potassium chloride + 134
163 mM hydrogen chloride), 2 (50 mM potassium chloride + 13 mM hydrogen chloride), 3
164 (50 mM potassium hydrogen phthalate + 22.3 mM hydrogen chloride), 4 (50 mM
165 potassium hydrogen phthalate + 0.1 mM hydrochloric acid), 5 (50 mM potassium
166 hydrogen phthalate + 22.6 mM sodium hydroxide), 6 (50 mM monopotassium
167 phosphate + 5.6 mM sodium hydroxide), 7 (50 mM monopotassium phosphate +
168 29.1 mM sodium hydroxide), 8 (50 mM tris hydroxymethyl aminomethane + 29.2 mM
169 hydrogen chloride) and 9 (50 mM tris hydroxymethyl aminomethane + 5.7 mM
170 hydrogen chloride). These stock solutions were used in experiments or were
171 adjusted using 1 M hydrochloric acid or 1 M sodium hydroxide to create the required
172 pH.

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Determination of raltegravir solubility

Raltegravir solubility was determined at 1 mM and 10 mM (estimated range of drug concentrations in the stomach and duodenum of the gut following raltegravir dissolution) in a pH range of 1 to 8. Solutions were mixed on a mechanical shaker (120 rpm, 37°C, 2 hours) and vortexed to allow maximum dissolution of raltegravir. Samples were then centrifuged to pellet undissolved drug (3000g, 10 minutes, 22 °C) and the supernatant carefully removed. Raltegravir concentrations in the supernatant were determined using LC-MS/MS.

Determination of raltegravir lipophilicity

Raltegravir lipophilicity was determined across a physiologically relevant pH range of 1 to 9 using the octanol:water Shake Flask Method. The organic solvent used was either 1-octanol, which allows hydrogen bonding, or cyclohexane, which does not allow hydrogen bonding. The aqueous and organic solvents were mutually saturated on a mechanical shaker (240 rpm, 24 hours, 22 °C) before use. Raltegravir was added to the aqueous solvent at 10 µM (a concentration ensuring complete solubility in all pH solutions) before combining the aqueous and organic solvents in a 1:1 ratio and shaking the mixtures for 30 minutes. Mixtures were centrifuged (800 g, 30 minutes, 22 °C) and a sample taken from the aqueous compartment for LC-MS/MS analysis. Calculation of the apparent logP was based on the following equation:

$$\text{Apparent logP} = \log \left(C_{organic} / C_{aqueous} \right)$$

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196 Where $C_{aqueous}$ is the concentration of raltegravir in the aqueous solvent and $C_{organic}$
197 is the concentration of raltegravir in the organic solvent (estimated by deducting
198 raltegravir in the aqueous compartment from the total amount in the mixture).
199
200 **Determination of raltegravir pKa**
201 Raltegravir pKa was determined using UV spectroscopy. Raltegravir was prepared in
202 buffered pH solutions to a final concentration of 8 μM (a concentration giving an
203 adequate signal for quantification). The buffered pH solutions ranged between pH
204 3.5 and 9.5. Drug solutions were added to UV cells which were then placed in a UV
205 spectrophotometer (Perkin Elmer lambda 25 UV-vis) and allowed to acclimatize
206 (25°C, 5 minutes). Following this, the UV-vis spectra were measured between 200
207 nm and 500 nm. The absorbance values were recorded at 300 nm (absorbance peak
208 predominant at lower pH) and 333 nm (absorbance peak predominant at higher pH).
209 For each pH the absorbance at 333 nm was divided by the absorbance at 300 nm
210 and plotted to calculate the pKa.
211
212 **Cell culture**
213 Caco-2 cells were maintained in cell culture (37°C, 5% CO_2) by passaging at 70%
214 confluence using cell culture medium (Dulbecco's Modified Eagle Medium (DMEM),
215 15% FCS). The passage number of the cells used in this study was between 25 and
216 35. Caco-2 monolayers were cultured as previously described (18) and were
217 subsequently used to determine the effects of pH, metal salts and omeprazole on
218 raltegravir monolayer permeability. Briefly, confluent Caco-2 cells were seeded onto
219 polycarbonate membrane transwells at a density of 5×10^5 cells / cm^2. Media was
220 replaced initially after 24 hours and then every 48 hours. Plates were used in the

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experiments twenty one days after seeding. Monolayer integrity was checked on the day of the experiment using a MillicellERS (Millipore) to determine the trans-epithelial electrical resistance (TEER) across the monolayer. A TEER of >600 was deemed acceptable. In addition, radiolabelled [^{14}C] mannitol was added to separate wells on each plate (n = 3) to confirm monolayer integrity. [^{14}C] mannitol samples were analysed by liquid scintillation counting (Beckman TRI-CARB®) and plates were only used for experiments if the average apparent permeability of mannitol was less than 1 cm x 10^{-6} s^{-1}.

Impact of pH on raltegravir cell monolayer permeability

On the day of study, the TEER was assessed and the media in each plate was replaced with the appropriate pH-buffered incubation solutions. The pH in the basolateral compartments was maintained at pH 7.4 (HBSS containing 25 mM HEPES) and the pH in the apical compartments was maintained at pH 5, 6, 6.5 (HBSS containing 10 mM MES), 7, 7.4, 8 (HBSS containing 25 mM HEPES) or 8.5 (HBSS containing 10 mM Tricine). Compartments were allowed to equilibrate (37°C, 30 minutes). The incubation buffer in the apical (for apical to basolateral transport) and basolateral (for basolateral to apical transport) compartments were replaced with the appropriate incubation buffer containing raltegravir (50 µM) and plates were incubated (37°C, 5% CO_2). A concentration of 50 µM raltegravir, which has been shown to be non-toxic to Caco-2 cells in previous studies (18), was used to ensure complete dissolution of drug at all pH solutions (as predicted by the solubility data) and to ensure drug concentrations in receiver compartments were sufficiently high to be quantifiable by LC-MS/MS. Samples were taken from the receiver compartments at 0, 30, 60, 90, and 120 minutes and replaced with fresh incubation buffer of the

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correct pH. Samples were analysed using LC-MS/MS. Results were used to determine apparent permeability (P_{app}, cm x 10^{-6} s^{-1}) for each direction and to determine the efflux ratio, which is the ratio of basolateral to apical P_{app} (B-to-A) compared with apical to basolateral P_{app} (A-to-B). P_{app} was calculated using the following equation as described previously (6):

$$P_{app} = \frac{(dQ / dt) \times v}{A \times C_0}$$

Where **dQ / dt** is the change in drug concentration in the receiver compartment over time (nM / s); **v** is the volume in the receiver compartment (mL); **A** is the total surface area of the transwell membrane (cm^2); $\mathbf{C_0}$ is the initial drug concentration in the donor compartment (nM); and $\mathbf{P_{app}}$ is the apparent permeability (cm / s).

Impact of divalent and monovalent metals on raltegravir cell monolayer permeability

On the day of study, the TEER was assessed and the media in each plate was replaced with the appropriate pH-buffered incubation solution. The pH in the basolateral compartments was maintained at pH 7.4 (HBSS without calcium chloride or magnesium sulphate (SIGMA code: H6648) containing 25 mM HEPES) and the pH in the apical compartments was maintained at pH 5 (HBSS without calcium chloride or magnesium sulphate containing 10 mM MES) or pH 7.4 (HBSS without calcium chloride or magnesium sulphate containing 25 mM HEPES). In the apical compartments at pH 5, magnesium chloride (1 mM, 10 mM or 25 mM), magnesium sulphate (25 mM), calcium chloride (25 mM) or potassium chloride (25 mM) were

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added. In the apical compartments at pH 7.4, magnesium chloride (1, 10 or 25 mM) was added. A maximum concentration of 25 mM was used for magnesium chloride as higher concentrations showed Caco-2 cell toxicity (data not shown). Control apical compartments at pH 5 and pH 7.4 were also used which had no added metal salts other than those in the original buffer. The pH in the basolateral compartments was maintained at pH 7.4 and had no added metal salts other than those in the original buffer. A concentration of 1 µM was used for all test compounds in order to maximise the metal to drug ratio. Lopinavir was used as a negative control as it is not believed to bind to metals. The incubation buffer in the apical (for A-to-B transport) and basolateral (for B-to-A transport) compartments were replaced with the appropriate incubation buffer containing radiolabelled [^{3}H] raltegravir (1 µM, 0.5 µCi / mL) or lopinavir (1 µM, 0.5 µCi / mL) and plates were incubated (37°C, 5% CO_2). Samples were taken from the receiver compartments at 0 and 30 minutes and were analysed by liquid scintillation counting. The P_{app} and efflux ratios were calculated as described in the previous section.

Impact of omeprazole on raltegravir cell monolayer permeability

For induction studies using transwells, the cell monolayers were incubated with omeprazole (10 µM) for the last three days of the twenty one day monolayer maturation. On the day of the experiment, the TEER was assessed and the media in each plate was replaced with warm incubation buffer (HBSS containing 25 mM HEPES, pH 7.4) and allowed to equilibrate (37°C, 30 minutes).

For inhibition studies the incubation buffer contained omeprazole (20 µM). A concentration of 20 µM omeprazole was used for investigations as lower

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296 concentrations are known to inhibit CYP2C9 and CYP2C19 *in vitro* (16). The
297 incubation buffer in the apical (for A-to-B transport) and basolateral (for B-to-A
298 transport) compartments were replaced with incubation buffer containing the test
299 substrate raltegravir (1 µM) with or without 20 µM omeprazole and plates were
300 incubated (37°C, 5% CO_2). A concentration of 1 µM raltegravir was used to avoid
301 saturation of drug transporters (11). Samples were taken from the receiver
302 compartments at 0 and 60 minutes and were analysed by liquid scintillation counting
303 (Beckman TRI-CARB®). The P_{app} and efflux ratios were calculated as described in
304 the previous section.
305
306 **Cellular accumulation**
307 Caco-2 cells were seeded (5 x 10^4 cells/mL) onto 6-well plates and grown for 5 days
308 to allow plate surface coverage (DMEM, 15% FBS, 37°C, 5% CO_2). Media was
309 removed and cells were washed with warm HBSS and replaced with the appropriate
310 pH-buffered incubation solution and allowed to equilibrate (37°C, 15 minutes). The
311 pH in the wells was fixed at either pH 5, 6 (HBSS containing 10 mM MES), 7 or 8
312 (HBSS containing 25 mM HEPES). The test substrate raltegravir (1 µM) was added
313 to the wells and plates were incubated (37°C, 5% CO_2, 10 minutes). A concentration
314 of 1 µM raltegravir was used to avoid saturation of drug transporters (11). A separate
315 incubation was undertaken where cells were pre-incubated (DMEM, 15% FBS, 37°C,
316 5% CO_2) prior to raltegravir addition with the potent non-competitive ABCB1 inhibitor
317 tariquidar (300 nM, 30 minutes), which was also included during the 10 minutes of
318 raltegravir incubation. Following incubation, an extracellular sample was removed for
319 analysis, wells were washed three times with ice cold HBSS and 500 µL tap water
320 was added to each empty well to lyse cells. Plates were frozen at minus 20°C

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321 overnight to aid removal of cells. Plates were thawed and 500 µL acetonitrile added
322 to each well to release drug from protein. The well contents were transferred to
323 separate 1.5 mL tubes for centrifugation (10 minutes, 3000 g, 22°C) and supernatant
324 was removed. Supernatant was vacuum dried and reconstituted in HPLC grade
325 water for LC-MS/MS analysis.
326
327 **LC-MS/MS analysis**
328 Samples from all studies other than from cell accumulation studies could be directly
329 injected into the LC-MS/MS after dilution with HPLC grade water. Samples from cell
330 accumulation studies were prepared as described in the cellular accumulation
331 method section. The LC-MS/MS system used for sample analysis consisted of an
332 autosampler model Surveyor, and LCQ DecaXP ion trap detector (Thermo, UK).
333 Chromatographic separation was performed at 30°C on a Fortis C-18 3 µM column
334 (50 X 2.1 mm i.d., Fortis technologies, UK). Mobile phases were solution A (95%
335 HPLC grade water, 5% acetonitrile, 0.05% formic acid) and solution B (10% HPLC
336 grade water, 90% acetonitrile, 0.05% formic acid) and flow rate was 0.4 mL / minute.
337 Separation was achieved with a gradient elution beginning with 80% solution A and
338 20% solution B. Solution B was gradually increased to 100% over 0.5 minutes and
339 maintained for a further 2 minutes. Solution A was increased to 80% over 0.1
340 minutes and maintained for 3.9 minutes, giving a total run time of 6.5 minutes. The
341 retention time of raltegravir was 4.78 minutes and the lowest limit of quantification
342 was 31.25 ng/mL. High QC (2000 ng/mL) had an inter-day and intra-day accuracy of
343 98.2% and 97.1%, respectively, and an inter-day and intra-day precision of 97.0%
344 and 93.1%, respectively. Medium QC (200 ng/mL) had an inter-day and intra-day
345 accuracy of 96.8% and 99.1%, respectively, and an inter-day and intra-day precision

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of 89.1% and 89.2%, respectively. Low QC (100 ng/mL) had an inter-day and intra-day accuracy of 96.5% and 92.8%, respectively, and an inter-day and intra-day precision of 90.0% and 95.3%, respectively. All QC gave higher than 85% accuracy and precision in accordance with FDA guidelines (23) and the linear range for raltegravir quantification was 31.25-1000 ng/mL.

Statistical Analysis

Data were analysed using PASW 18 for Windows. All data were tested for normality using the Shapiro-Wilk test. An independent t-test was used to determine significance of normally distributed data. The Mann Whitney U test was used for all other data. A two-tailed p value above 0.05 was accepted as being statistically significant.

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Results

Raltegravir solubility

Figure 1A shows raltegravir solubility over a range of buffers ranging from pH 1 to 8. A concentration of 1 mM raltegravir was fully soluble across the pH range. However, 10 mM raltegravir was only fully soluble at pH 6.8, 6.9, 7 and 8 and achieved a mean supernatant concentration of 8.0 mM at pH 6.6, 6.3 mM at pH 6.4, 5.0 mM at pH 6.2, 3.7 mM at pH 6 and around 3 mM at pH 5 and below.

Raltegravir lipophilicity

When using cyclohexane as the organic solvent, raltegravir remained predominantly in the aqueous compartment (~90%) in all pH solutions, whereas using octanol resulted in low raltegravir concentrations (~7%) in the aqueous compartments of pH 5 or less (Figure 1B). Therefore when using octanol as the organic solvent, raltegravir apparent logP was stable between aqueous pH 1 and 5 but decreased from 1.06 to -1.29 between pH 5 and 9 ($p<0.05$; Figure 1C). A negative logP is usually associated with poor cell membrane permeability (10).

Raltegravir pKa

Figure 1D shows the relative absorbance at two wavelengths (333 nm versus 300 nm) as a function of the pH of the buffer solution. The most substantial change in the curve occurs between pH 6 and 8. If it is assumed that this change in peak ratios is due to an alteration of the charge state of raltegravir, the pKa is calculated as pH 6.7.

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Impact of pH on raltegravir cell monolayer permeability

Figure 2A depicts the apical to basolateral raltegravir permeability through Caco-2 cell monolayers at varying apical pH values. Increasing the apical pH from 5 to 8.5 decreased the rate and extent of raltegravir monolayer permeability in the apical to basolateral direction ($p<0.05$). The P_{app} and efflux ratio of raltegravir at 60 minutes incubation is shown in Table 1. Raltegravir efflux ratio increased 12-fold as apical pH was increased from 5 to 8.5 ($p<0.05$). When both apical and basolateral pH was 7.4 the efflux ratio was 2.5, suggesting active transport in the basolateral to apical direction. However, reducing apical pH to 6 or below caused raltegravir permeability to predominate in the apical to basolateral direction, suggesting that pH has the potential to overcome the effect of active drug transport.

Impact of divalent and monovalent metals on raltegravir cell monolayer permeability

All P_{app} and efflux ratio calculations were made using samples taken after 30 minutes of incubation and sink conditions were maintained at this time point. A positive correlation between concentration of magnesium chloride in the apical compartment and raltegravir efflux ratio is shown in Figure 2B. When the apical compartment was pH 7.4, raltegravir efflux ratio was significantly increased when comparing control wells with no additional metal salt (efflux ratio = 1.3) to wells containing 1 mM (efflux ratio = 1.6, $p<0.05$), 10 mM (efflux ratio = 3.4, $p<0.05$) or 25 mM (efflux ratio = 3.7, $p<0.05$) magnesium chloride. Lopinavir efflux ratio was unaltered when comparing control wells with no additional metal salt (efflux ratio = 5.1) to wells containing 25 mM magnesium chloride (efflux ratio = 5.4, $p = 0.83$) illustrating that the effect of

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409 magnesium chloride on raltegravir cellular permeability was not a result of general
410 changes in monolayer integrity.
411
412 When the apical compartment was pH 5, raltegravir efflux ratio was unchanged when
413 comparing control wells with no additional metal salt (efflux ratio = 0.8) to wells
414 containing 1 mM magnesium chloride (efflux ratio = 0.7, p = 0.28), but a significant
415 increase in efflux ratio was observed with addition of 10 mM (efflux ratio = 1.1,
416 $p<0.05$) or 25 mM (efflux ratio = 1.9, $p<0.05$) magnesium chloride. Also, the effects
417 of magnesium in a different salt form (magnesium sulphate), an additional divalent
418 metal salt (calcium chloride) and a monovalent metal salt (potassium chloride) were
419 investigated. Raltegravir efflux ratio was significantly increased when comparing
420 control wells with no additional metal salt (efflux ratio = 0.8) to wells containing 25
421 mM magnesium sulphate (efflux ratio = 1.6, $p<0.05$) or 25mM calcium chloride (efflux
422 ratio = 1.2, $p<0.05$). The efflux ratio was unaltered when 25 mM potassium chloride
423 was added to the apical compartment (efflux ratio = 0.8, p = 0.83). This supports the
424 hypothesis that divalent metals, but not monovalent metals, have the potential to
425 affect raltegravir cell membrane permeability.
426
427 **Impact of omeprazole on raltegravir cell monolayer permeability**
428 Figure 2C depicts the efflux ratio of 1 µM raltegravir through Caco-2 cell monolayers
429 in the presence and absence of omeprazole as an inhibitor (20 µM) or as an inducer
430 (72 hour pre-incubation with 10 µM omeprazole). All P_{app} and efflux ratio calculations
431 were made using samples taken after 60 minutes of incubation and sink conditions
432 were maintained. In inhibition studies, there was no significant difference in
433 raltegravir efflux ratio between control cells and cells co-incubated with 20 µM

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434 omeprazole (efflux ratio of 2.7 versus 2.6; p=0.83). Similarly, in induction studies
435 there was no significant difference in raltegravir efflux ratio between control cells and
436 cells pre-incubated for 72 hours with 10 μM omeprazole (efflux ratio of 2.7 versus
437 2.6; p=0.51).
438
439 **Impact of pH and ABCB1 inhibition on raltegravir cellular accumulation**
440 Figure 2D depicts the accumulation of raltegravir in Caco-2 cells using various pH
441 buffers and using tariquidar to inhibit ABCB1. Raltegravir accumulation in Caco-2
442 cells increased 3.4-fold when incubation buffer pH was decreased from 8 to 5
443 ($p<0.05$). This pH-related increase in raltegravir accumulation was also observed in
444 cells treated with the ABCB1 inhibitor tariquidar (3.3-fold decrease; $p<0.05$).
445 Inhibiting ABCB1 led to increased raltegravir accumulation at pH 5 (1.4-fold; $p<0.05$),
446 6 (1.5-fold; $p<0.05$), and 7 (1.4-fold; $p<0.05$) but not at pH 8 ($p=0.08$). These results
447 suggest that pH impacts upon cellular permeability of raltegravir to a greater extent
448 than ABCB1 transport and that ABCB1 transport of raltegravir is independent of pH.
449

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450 **Discussion**

451 In this study the influence of pH on raltegravir solubility, lipophilicity and cellular
452 permeability was investigated. Raltegravir exhibited solubility of less than 10 mM at
453 pH 6.6 and below. It is likely that the drug obtains a negative charge at higher pH by
454 deprotonation of the hydroxyl group at the 5-position of the 6-oxo-1,6-
455 dihydropyrimidine ring. This negative charge would dramatically increase the
456 solubility of the drug in aqueous buffer. Additionally, raltegravir logP was shown to
457 decrease as pH is increased above 6, presumably due to the introduction of a
458 charge to the drug. The solubility and lipophilicity data are supported by our UV
459 spectroscopy study, where raltegravir pKa was calculated at 6.7. This pKa is located
460 within the pH range that will be encountered by the drug during absorption in the GI
461 tract. This offers us a convincing explanation of the intra- and inter-patient variability
462 of raltegravir PK raltegravir in healthy and HIV-1-infected subjects (3).

463

464 In experiments assessing raltegravir cellular permeability, raltegravir was less able to
465 cross a Caco-2 cell monolayer as the incubation buffer pH was increased from 5 to
466 8.5. This is most likely due to the introduced charge at the active site, preventing the
467 drug from passing through the phospholipid bilayer of the cell membrane. Similar
468 results were seen in accumulation studies, where less raltegravir was present in the
469 cells when pH was increased from 5 to 8. ABCB1 inhibition had less impact on
470 raltegravir intracellular concentrations than changes in extracellular pH. Permeability
471 and accumulation were assessed using raltegravir concentrations from 1 μM to 50
472 μM and our solubility studies show that the drug is fully soluble at all pH values at
473 these concentrations. Therefore, the introduction of a charge to raltegravir by
474 increasing pH could have opposing consequences depending on the concentration

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475 of the drug. At high drug concentrations the introduced charge is predicted to
476 increase dissolution and therefore absorption. Conversely, at lower concentrations
477 solubility is unlikely to be a problem and therefore the introduced charge may reduce
478 the rate of absorption.

479

480 In previous clinical studies, co-administration of omeprazole and famotidine resulted
481 in an increase in raltegravir C_{max} (24). This may result from the predicted increased
482 solubility of raltegravir in the stomach and the duodenum, where drug concentrations
483 would be highest. The C_{12hr} of raltegravir was only slightly higher or unchanged when
484 taken with omeprazole or famotidine (24). It is tempting to speculate that over time
485 raltegravir dissolution normalises in all subjects and the benefit of increased gastric
486 pH is overcome. Inhibition and induction studies with omeprazole indicated that there
487 were no direct effects on raltegravir cellular permeability, indicating that the effect of
488 omeprazole most likely results from its pH-altering properties.

489

490 Ingestion of a meal has been shown to result in an increase in gastric pH (5), which
491 would be predicted to increase raltegravir solubility. However, only high fat meals
492 have been shown to increase raltegravir exposure with low fat meals resulting in a
493 reduction (1). It is possible that a high fat meal may dilute stomach acid to a greater
494 extent or that the fat in the meal could increase the solubility of raltegravir.

495

496 Raltegravir cellular permeability decreased in the presence of the divalent cations
497 magnesium and calcium in the incubation medium. This decrease was not found
498 when the monovalent cation potassium was used. Raltegravir may bind to the

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divalent metals and form a metal-drug complex which is unable to cross the cell membrane. It is important to note that binding of raltegravir to a divalent metal (magnesium) is an essential prerequisite for inhibition of the HIV integrase enzyme (17). Antacids containing magnesium caused no significant change in raltegravir C_{max} or AUC but did reduce C_{12hr}, resulting in 75% of patients having C_{12hr} less than the IC_{95} (15). The impact of antacids may be explained by a combination of the effects of pH and metal binding. We hypothesise that C_{max} remains unchanged while raltegravir solubility improves with increased pH but absorption is inhibited by magnesium binding. At later time points, when raltegravir solubility is no longer an issue, the elevated presence of magnesium in the gut may reduce the amount of raltegravir being absorbed, thus reducing raltegravir C_{12hr}. If true, co-administration of products containing polyvalent metal cations that do not alter gastric pH (e.g. multivitamin tablets) would be expected to reduce raltegravir exposure. This is certainly now worthy of empirical determination.

These data may also have implications for newer integrase strand transfer inhibitors, elvitegravir and dolutegravir. Elvitegravir and dolutegravir exposure have been shown to be reduced when taken with antacids containing magnesium and aluminium, being less marked when taken 2 hours before the antacid (19) (21). In healthy subjects, elvitegravir and dolutegravir absorption have also been shown to be influenced by food according to fat content (26) (9) and it is recommended that elvitegravir is taken with food (20). Interestingly, dolutegravir exposure has also been shown to be moderately reduced when taken with a multivitamin containing magnesium, calcium, iron, zinc and copper (19).

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524 In conclusion, the physicochemical properties of raltegravir are heavily influenced by
525 environmental pH. Both pH and polyvalent metals have the potential to alter the
526 pharmacokinetics of raltegravir and these data help provide a rationale for the
527 variability in raltegravir exposure seen in patients. The evaluation of how divalent
528 metal-containing products, such as multivitamins that do not affect gastric pH, alter
529 raltegravir pharmacokinetics in patients is now justified. A comprehensive knowledge
530 of the mechanisms that underpin variability in disposition will help optimise future
531 therapy with raltegravir.
532

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Figure 1

Figure 1A. Raltegravir solubility at 1 mM (grey squares ▪) and 10 mM (black circles ●) in a range of pH solutions. Data are expressed as mean raltegravir dissolved in solution (mM; n ≥ 3 experimental replicates) ± SD.

Figure 1B. Partition of raltegravir (10 µM) between cyclohexane and water (grey squares ▪) and octanol and water (black circles ●) at different pH solutions. Data are expressed as mean percentage of raltegravir in water (% of total; n = 4 experimental replicates; n = 3 biological replicates) ± SD.

Figure 1C. Apparent logP of raltegravir (10 µM) using octanol and water at different pH solutions. Data are expressed as mean log of raltegravir partition (logP; n = 4 experimental replicates; n = 3 biological replicates)) ± SD.

Figure 1D. Determination of raltegravir pKa using UV spectroscopy. Data are expressed as relative absorbance at two wavelengths (333 nm versus 300 nm) as a function of the pH of the buffer solution (n = 1 experimental replicate).

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Figure 2

Figure 2A. Time course experiment showing A-to-B permeation of raltegravir (50 μM) in Caco-2 monolayers over 120 minutes. Results are presented when using a range of apical pH buffers shown in the figure key. The basolateral pH was maintained at 7.4. Data are expressed as mean raltegravir accumulation in the basolateral (receiver) compartment (μM; n = 3 experimental replicates).

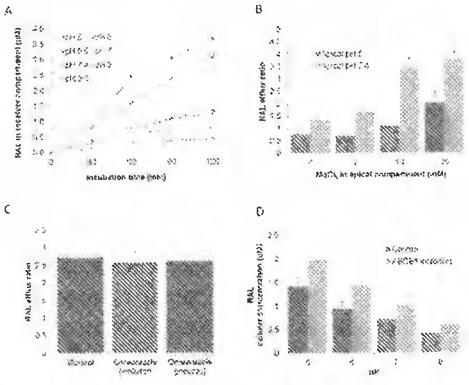
Figure 2B. Efflux ratio of raltegravir (1 μM) in Caco-2 monolayers using a range of magnesium chloride concentrations in the apical compartment. The apical compartment was maintained at pH 5 or pH 7.4 and the basolateral compartment was maintained at pH 7.4.

Figure 2C. Efflux ratio of raltegravir (1 μM) in the presence of omeprazole (inhibitor study; 20 μM) or with cells pre-incubated with omeprazole for 3 days (induction study; 10 μM). Data for Figures 2B and 2C are expressed as mean drug efflux ratio (B-to-A / A-to-B; n = 3 experimental replicates) ± SD.

Figure 2D. Accumulation of raltegravir (1 μM) in Caco-2 cells at extracellular pH of 5 to 8, with and without ABCB1 inhibitor tariquidar (300 nM). Data are expressed as mean intracellular raltegravir (μM; n = 3 experimental replicates) ± SD.

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Tables

Table 1. The effect of pH on raltegravir (50 μM) permeability using a Caco-2 monolayer. Column one gives the range of apical pH buffers used (basolateral pH was maintained at 7.4). Columns two and three give apparent permeability of raltegravir in the A-to-B and B-to-A directions, respectively. Data are presented as mean P_{app} (cm x 10^{-6} / second, n = 3 experimental replicates) ± SD. Column four gives the efflux ratio of raltegravir ($P_{app\ B\text{-}to\text{-}A}$ / $P_{app\ A\text{-}to\text{-}B}$). Column five compares the efflux ratio at pH 5 with other pH values (a significant difference was deemed to have a p value of <0.05).

pH of apical compartment	A-to-B P_{app} (cm x 10^{-6} / second)	B-to-A P_{app} (cm x 10^{-6} / second)	Efflux ratio	Efflux ratio significance compared to pH5
5	27.3 ± 1.2	11.9 ± 1.5	0.4	-
6	17.6 ± 1.7	13.1 ± 2.3	0.7	p<0.05
6.5	9.2 ± 1.1	14.5 ± 1.5	1.6	p<0.05
7	8.4 ± 1.2	14.5 ± 2.1	1.7	p<0.05
7.4	6.6 ± 0.8	16.4 ± 2.9	2.5	p<0.05
8	3.5 ± 0.5	13.8 ± 0.7	3.9	p<0.05
8.5	2.9 ± 0.3	14.1 ± 1.3	4.9	p<0.05

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
1147.P2F		
International application No	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2016/060989	8 November 2016 (08-11-2016)	9 November 2015 (09-11-2015)
Applicant		
GILEAD SCIENCES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 5
      [ ] as suggested by the applicant
      [X] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/060989

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/28 A61K31/513 A61K31/5365 A61K31/675
A61P31/18 A61K9/24 A61K31/553
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2015/196116 A1 (GILEAD SCIENCES INC [US]) 23 December 2015 (2015-12-23) abstract; claims 1, 12, 18-21	1-51
X,P	WO 2015/196137 A1 (GILEAD SCIENCES INC [US]) 23 December 2015 (2015-12-23) abstract; claims 1, 38, 44-48	1-51
X	WO 2014/100323 A1 (GILEAD SCIENCES INC [US]) 26 June 2014 (2014-06-26) cited in the application	34
Y	abstract; claims 1, 32, 33-46; examples 104-107; compounds 42, 45 page 36, paragraph 12-13 page 37, paragraph 8-12 page 38, lines 14, 20	1-51

-/--

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January 2017	24/01/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Madalinska, K

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/116720 A1 (GILEAD SCIENCES INC [US]) 8 August 2013 (2013-08-08)	35
Y	abstract; claims 21-32 page 82, lines 13-15 paragraphs [0337], [0338], [0342], [0344] - [0345], [0349], [0355] paragraphs [0340], [0347] -----	1-51
Y	WO 2015/022351 A1 (RATIOPHARM GMBH [DE]) 19 February 2015 (2015-02-19) abstract; claims 1-6, 8-10, 12-15 page 18, lines 7-22 page 19, lines 3-12 page 19, line 30 - page 20, line 12 page 22, line 31 - page 15, line 17 -----	1-51
Y	"Gilead and Tibotec finalize agreement on single-tablet HIV regimen", Thomson Reuters Drug News, 17 November 2011 (2011-11-17), XP055052007, Retrieved from the Internet: URL:https://integrity.thomson-pharma.com/integrity/xmlxsl/pk_ref_list.xml_show_ficha_ref?p_ref_id=1729357 [retrieved on 2013-02-01] abstract -----	1-51

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/060989

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1456 of 1915

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/060989

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP 2016528240 A	15-09-2016
		US 2016184332 A1	30-06-2016
		WO 2015022351 A1	19-02-2015

Information on Search Strategy - Pilot phase (see OJ 2015, A86)
The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number
PCT/US2016/060989

TITLE: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

APPLICANT: GILEAD SCIENCES, INC.

IPC CLASSIFICATION: A61K9/20, A61K9/28, A61K31/513, A61K31/5365, A61K31/675, A61P31/18, A61K9/24, A61K31/553

EXAMINER: Madalinska, K

CONSULTED DATABASES: WPI, EPODOC, CA, INTEGRITY, REAXYS, NPL

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61K9/2054, A61K9/2866, A61K31/513, A61K31/5365, A61K31/675, A61K9/209, A61K31/553

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:
A solid oral dosage, tablet, capsule, coated tablet, tenofoviral afenamide, emtricitabine), microcrystalline cellulose, croscarmellose, HIV infection, human immunodeficiency viral infection, AIDS

EPO FORM P04A42

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference	**FOR FURTHER ACTION**
see form PCT/ISA/220	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2016/060989	08.11.2016	09.11.2015

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/20 A61K9/28 A61K31/513 A61K31/5365 A61K31/675 A61P31/18 A61K9/24 A61K31/553

Applicant
GILEAD SCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Madalinska, K Telephone No. +49 89 2399-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

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Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-33, 36-51
	No:	Claims	34, 35
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-51
Industrial applicability (IA)	Yes:	Claims	1-51
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

D1 WO 2015/196116 A1

D2 WO 2015/196137 A1

D3 WO 2014/100323 A1

D4 WO 2013/116720 A1

D5 WO 2015/022351 A1

D6 Thomson Reuters Drug News, 2011, XP055052007

2 The relevant passages are those indicated in the search report, unless otherwise specified.

3 Claim 39 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability assessment will be carried out based on the alleged effects of the compounds searched in the International Search report.

It is further to be noted that the patentability of claim 39 can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

4 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 34-35 is not new in the sense of Article 33(2) PCT.

4.1 D3 discloses a tablet as a single dosage form comprising a compound of formula (I) including compounds 42 and 45 of D3.

Hence, claim 34 does not meet the requirements of Article 33(2) PCT for novelty.

4.2 D4 discloses a monolayer and bilayered tablet comprising in one single layer tenofovir alafenamide and emtricitabine compressed together.

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Hence, claim 35 does not meet the requirements of Article 33(2) PCT for novelty.

5 None of the documents in the prior art discloses a solid oral dosage form comprising a compound of formula I, tenofovir alafenamide and emtricitabine.

Hence, claims 1-33, 36-39 and 43-51 are considered as meeting the requirements of Article 33(2) PCT for novelty.

Furthermore, none of the documents in the prior art discloses a composition comprising 40-60mg of the compound of formula (I), 20-400 mg microcrystalline cellulose and 1-40 mg croscarmellose.

Hence, claims 40-42 are considered also as meeting the requirements of Article 33(2) PCT for novelty.

6 However, the Applicant should bear in mind the content of D1-D2 (cited under section VI) which could be held prejudicial to the novelty of all the claims during Regional or National examination phase(s).

7 The present application does not meet the criteria of Article 33(1) PCT because the subject-matter of claims 1-51 does not involve an inventive step in the sense of Article 33(3) PCT.

7.1 In general, it is not considered inventive (Article 33(3) PCT) to combine two or more active ingredients for treating a particular disease in the case where said two or more active agents are each known to be therapeutically effective alone in treating said particular disease. In this regard, it would normally be expected that such a composition of active agents would be more effective than either active agent alone. Exceptions to this general principle may be made if the new combination has a surprising property, e.g. synergistic therapeutic benefit, which could not have been fairly predicted on the basis of the prior art.

The compound of formula I is known to be therapeutically effective in the treatment of HIV (see documents D3). Its combination with another anti-HIV agent including tenofovir alafenamide and emtricitabine is also suggested in D3.

Tenofovir alafenamide and emtricitabine are also known to be effective in the treatment of HIV when used alone (D4) or in combination with other anti-HIV agents in a single dosage form (see D4-D6).

With reference to the possibility of a surprising technical effect, it is noted that the present application provides no example of the putative synergistic effect between compound of formula (I), tenofovir alafenamide and emtricitabine.

It should be noted that the unexpected or surprising effect that is alleged in support for such a demonstration must be made plausible over the whole scope of the claimed subject-matter. Thus, a surprising effect must be demonstrated for each and every embodiment of the claims.

As a result, the subject matter of claims 1-39, 41-51 does not meet the requirements of Article 33(3) PCT for inventive step.

7.2 D3 is considered as the closest prior art for the subject-matter of claim 40 and discloses an oral aqueous suspension of a compound 42 (compound of formula (I) as presently claimed) in Tween, HPMC in water.

The subject-matter of claim 40 differs from D3 in that the composition comprises microcrystalline cellulose and croscarmellose sodium.

There is no technical effect shown for the difference in the excipients if compared with D3.

The problem to be solved is thus provision of an alternative pharmaceutical formulation comprising a compound of formula (I).

However, the variation of the amount of drug and excipients belongs to common experimental design.

Hence, the characterising features of this claim would be regarded by the skilled man as being the result of normal development procedure and therefore, claim 40 is not considered as meeting the requirements of Article 33(3) PCT for inventive step.

Re Item VI

Certain documents cited

8 D1-D2 are cited under Rules 64.3 and 70.10 PCT.

Re Item VIII

Certain observations on the international application

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9 The subject-matter of claims 28-30 and 46-51 do not meet the requirements of Article 6 PCT because the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, namely in the form of release/dissolution profile/rate, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

10 The subject-matter of claims 34-35 is not clear (Article 6 PCT) because the first layer and the second layers are not defined.

For the purpose of the present opinion it is assumed that i) the first layer means a composition comprising a compound of formula (I) and ii) the second layer means a combination of tenofovir alafenamide and emtricitabine compressed together.

11 The approximate term "about" used in claims 4-5, 40, 42-44, 46-48 and 50 leaves the reader in doubt as to the exact meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

12 Although claims 7, 8, 9, 11, 12, 16, 43, 44 have been drafted as separate independent claims, it seems that they comprise all the features of claim 1 and they are therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).

13 Also claims 49, 50 and 51 comprise all the features of claim 46 and they are therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).

Thomson Reuters Drug News

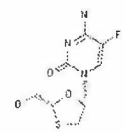
AIDS news article

Fri Sep 01 2017

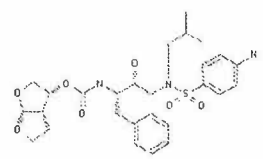
Gilead and Tibotec finalize agreement on single-tablet HIV regimen

Thu Nov 17, 2011 | Section: AIDS

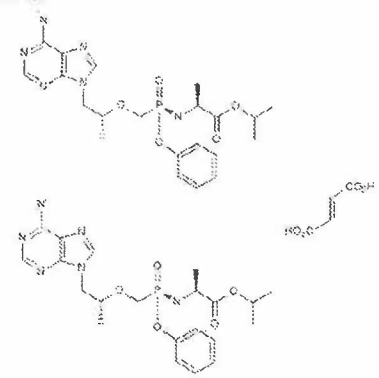
Gilead Sciences and Tibotec Pharmaceuticals recently entered into a licensing agreement for the development and commercialization of a single-tablet regimen containing Prezista(R) (darunavir) from Gilead's third-party combinations. GS-7340 and cobicistat. Under the agreement, Gilead will be responsible for the formulation, manufacturing, registration and, subject to regulatory approval, distribution and commercialization of the single-tablet regimen worldwide. Tibotec will have the right to co-detail the single-tablet regimen in certain major markets. The companies first entered into a collaboration in July 2009 for the development and commercialization of a single-tablet regimen containing Gilead's Truvada(R) (emtricitabine/tenofovir disoproxil fumarate) and Tibotec's Edurant(R) (rilpivirine hydrochloride) (see *Thomson Reuters Drug News*, July 27, 2009). The product was approved under the brand name Complera(R) (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) in the U.S. in August of this year (see *Thomson Reuters Drug News*, August 15, 2011). The two companies entered into an additional licensing agreement for the development of a fixed-dose combination containing darunavir and cobicistat, which was contingent upon the signing of the agreement to develop the darunavir combination. GS-7340 and cobicistat single-tablet regimen. Both agreements have now been finalized. Subject to regulatory approval, Tibotec will be responsible for the formulation, manufacturing, registration, distribution and commercialization of the darunavir and cobicistat fixed-dose combination worldwide. Separately, Gilead is evaluating cobicistat in three pivotal phase III studies, both as a stand-alone boosting agent for once-daily atazanavir sulfate, as well as part of the a fixed-dose single-tablet Quad (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) combination regimen for the treatment of HIV infection (*ClinicalTrials.gov* identifier NCT01401231). GS-7340 is a novel prodrug of tenofovir, the active agent in the company's HIV drug Viread(R) (tenofovir disoproxil fumarate). Gilead plans to initiate a proof of study of GS-7340 early in 2012 (Gilead Sciences News Release).



Emtricitabine

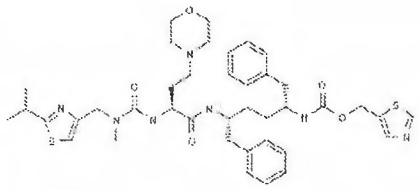


Darunavir



GS-7340

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Cobicistat

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I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: October 6, 2017 Signature: /Abigail Edesan/ (Abigail Edesan)

Docket No.: 1147.PC
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Benjamin Micah Collman et al.

Application No.: 15/346,335 Confirmation No.: 1307

Filed: November 8, 2016 Art Unit: 1615

For: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus Examiner: J. N. Worsham

INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed before the mailing date of a first Office Action on the merits (37 C.F.R. § 1.97(b)(3)).

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), copies of U.S. patents and U.S. patent application publications are not submitted. Submitted herewith are copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

A concise explanation of relevance of the non-English references listed on form PTO/SB/08 is given.

804800.1

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to the patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 07-1250, under Order No. 1147.PC from which the undersigned is authorized to draw.

Dated: October 6, 2017

Respectfully submitted,

By /Mary J. Edwards/
Mary J. Edwards
Registration No.: 55,140
GILEAD SCIENCES, INC.
Correspondence Customer Number: 25000
(650) 522-1816
Attorney For Applicant

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/346,335	Filing Date 11/08/2016	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 = *		X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 = *		X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/18/2017	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 46	Minus	** 46	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 12	Minus	*** 12	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LDRC
ANDREW JAMES JR

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C	1307

25000 7590 01/24/2018

GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CALIFORNIA 94404

EXAMINER	
WORSHAM, JESSICA N	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
01/24/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPDocketing@gilead.com
IPUS2@gilead.com

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 15/346,335	Applicant(s) Collman et al.	
	Examiner JESSICA WORSHAM	Art Unit 1615	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____

2a)☐ This action is **FINAL.** 2b)☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-6,9-35 and 39-51 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☐ Claim(s) _____ is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☑ Claim(s) 1-6,9-35 and 39-51 are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____

4) ☐ Other: _____.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
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Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Detailed Action

Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-6, 9-30, and 40-51, drawn to a solid oral dosage form comprising the compound of Formula 1, classified in A61K9/209.

II. Claims 31-35, drawn to a method of producing a tablet, classified in A61K9/2095.

III. Claim 39, drawn to a method of therapeutic treatment of HIV infection, classified in A61K9/0053.

The inventions are independent or distinct, each from the other because:

Inventions I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the product can be made by another materially different process, i.e., production of a monolayer tablet instead of a multi-layer tablet.

Inventions I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP

§ 806.05(h). In the instant case the process for using the product can be practiced with another materially different product, i.e., a mono-layer or multi-layer tablet.

Inventions II and III are directed to related processes. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the processes have a materially different design, mode of operation, or function since Group II is directed to a method of making a product and Group III is directed to a method of using the product. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Restriction for examination purposes as indicated is proper because all the inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention.**

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product/apparatus claims. **Failure to do so may result in no rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Correspondence

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to JESSICA WORSHAM whose telephone number is (571)270-7434. The examiner can normally be reached on Monday-Friday (8-5).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Wax can be reached on 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JESSICA WORSHAM/
Primary Examiner, Art Unit 1615

To: IPDocketing@gilead.com,IPUS2@gilead.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 25000

Jan 24, 2018 03:21:33 AM

Dear PAIR Customer:

GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 25000 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

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Application	Document	Mailroom Date	Attorney Docket No.
15346335	CTRS	01/24/2018	1147.P2C

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: April 24, 2018 Signature: /David Castro/
(David Castro)

Docket No.: 1147.P2C
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Benjamin Micah Collman et al.

Application No.: 15/346,335		Conf. No.:	1307
Filed: November 8, 2016		Art Unit:	1615
For:	THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS	Examiner:	Jessica N. Worsham

AMENDMENT & RESPONSE TO RESTRICTION REQUIREMENT

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

This communication is submitted in response to the Restriction Requirement dated January 24, 2018.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

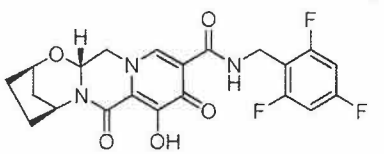
693945.1

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of the claims in the application:

1. (Currently Amended) A ~~solid oral dosage form~~ tablet comprising 50 mg of the compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

2. (Currently Amended) The ~~solid oral dosage form~~ tablet of claim 1, wherein the ~~dosage form~~ tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

3. (Currently Amended) The ~~solid oral dosage form~~ tablet of claim 1 or 2, wherein the ~~dosage form~~ tablet comprises 52 mg of the sodium salt of the compound of Formula I and 28 mg tenofovir alafenamide hemifumarate.

4. (Currently Amended) The ~~solid oral dosage form of claim 2~~ tablet of any one of claims 1-3, wherein the ~~dosage form~~ tablet has a total weight of less than about 800 mg.

5. (Currently Amended) The ~~solid oral dosage form of claim 2~~ tablet of any one of claims 1-3, wherein the ~~dosage form~~ tablet has a total weight of less than about 730 mg.

6-25 (Canceled)

26. (Currently Amended) The tablet of ~~claim 20~~ any one of claims 1-5, wherein the tablet contains less than about 15% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

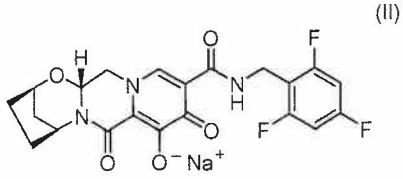
27. (Currently Amended) The tablet of ~~claim 20~~ any one of claims 1-5, wherein the tablet contains less than about 11% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

28-51 (Canceled)

52. (New) The tablet of any one of claims 1-5, 26, and 27, wherein the tablet is a coated tablet.

53. (New) The tablet of any one of claims 1-5, 26, and 27, comprising:

(II)



(i) a first layer including:

Ingredient	Mass (mg/tablet)
Compound of Formula II	52.5 (*equivalent to 50 mg of the Compound of Formula I*)
Microcrystalline cellulose	246.3
Croscarmellose sodium	19.4
Magnesium Stearate	4.9

(ii) a second layer including:

Ingredient	Mass (mg/tablet)
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28 (*equivalent to 25 mg tenofovir alafenamide*)

Microcrystalline cellulose	113.2
Croscarmellose sodium	30.2
Magnesium Stearate	5.7

and (iii) a film coating.

54. (New) The tablet of any one of claims 1-3, wherein the tablet has a total weight of less than about 1000 mg.

REMARKS

Claims 1-6, 9-35, and 39-51 are pending. With this amendment, claims 6, 9-25, 28-35, and 39-51 have been canceled without prejudice or disclaimer. Claims 1-5, 26, and 27 have been amended. Claims 52-54 are newly added. No new matter is added. Thus, upon entry of the amendment, claims 1-5, 26, 27, and 52-54 will be pending.

Claim 1 has been amended to focus on a tablet comprising the compound of Formula I. Support for this amendment is found, for example, in paragraphs [0021] and [0054] of the specification as-filed, and original claim 6. Dependent claims 2-5 have been amended to recite "tablet", accordingly.

Claim 1 has been further amended to recite specific amounts of the tablet components. Support for this amendment is found, for example, in paragraphs [0009] and [0332] (table) of the specification as-filed, and original claim 6.

Claims 26 and 27 have been amended so as not to depend from canceled claims.

Support for new claims 52-54 is found throughout the specification and claims as-filed. For example, support for new claim 52 is found in paragraphs [0013] and [0072], and original claim 7; support for new claim 53 is found in paragraph [0332] (table).

The Office has required election of one of the following groups of claims:

Group I:	Claims 1-6, 9-30 and 40-51
Group II:	Claim 31-35
Group III:	Claim 39

Applicant hereby elects Group I for examination. Claims 1-5, 26, 27, and 52-54 read on the elected subject matter.

The claims are now in condition for allowance, for which action is hereby requested.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 07-1250, under Order No. 1147.P2C from which the undersigned is authorized to draw.

Dated: April 24, 2016

Respectfully submitted,

By: /Mary J. Edwards/
Mary J. Edwards
Registration No.: 55,140
GILEAD SCIENCES, INC.
Correspondence Customer Number: 25000
(650) 522-1816
Attorney For Applicant

Electronic Patent Application Fee Transmittal	
Application Number:	15346335
Filing Date:	08-Nov-2016
Title of Invention:	Therapeutic Compositions for Treatment of Human Immunodeficiency Virus
First Named Inventor/Applicant Name:	Benjamin Micah Collman
Filer:	Mary J. Edwards/David Castro
Attorney Docket Number:	1147.P2C
Filed as Large Entity	

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
MULTIPLE DEPENDENT CLAIMS	1203	1	820	820
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	200	200
Miscellaneous:				
		Total in USD ($)		**1020**

Electronic Acknowledgement Receipt	
EFS ID:	32432630
Application Number:	15346335
International Application Number:	
Confirmation Number:	1307
Title of Invention:	Therapeutic Compositions for Treatment of Human Immunodeficiency Virus
First Named Inventor/Applicant Name:	Benjamin Micah Collman
Customer Number:	25000
Filer:	Mary J. Edwards/David Castro
Filer Authorized By:	Mary J. Edwards
Attorney Docket Number:	1147.P2C
Receipt Date:	24-APR-2018
Filing Date:	08-NOV-2016
Time Stamp:	17:23:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1020
RAM confirmation Number	042518INTEFSW00004723071250
Deposit Account	071250
Authorized User	David Castro
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		1147P2C_2018-04-24_Response-to-Restriction-Requirement.PDF	55020 3cd3051e7d6746f6639ee78ad9fa17ac373b1f112	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response to Election / Restriction Filed	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	6

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	32331 940a2ba83a0f51a2551553abd132e891b098826a1af46	no	2

Warnings:

Information:

Total Files Size (in bytes):	87351

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

REMARKS

Claims 1-6, 9-35, and 39-51 are pending. With this amendment, claims 6, 9-25, 28-35, and 39-51 have been canceled without prejudice or disclaimer. Claims 1-5, 26, and 27 have been amended. Claims 52-54 are newly added. No new matter is added. Thus, upon entry of the amendment, claims 1-5, 26, 27, and 52-54 will be pending.

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The Office has required election of one of the following groups of claims:

Group I:	Claims 1-6, 9-30 and 40-51
Group II:	Claim 31-35
Group III:	Claim 39

Applicant hereby elects Group I for examination. Claims 1-5, 26, 27, and 52-54 read on the elected subject matter.

The claims are now in condition for allowance, for which action is hereby requested.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 07-1250, under Order No. 1147.P2C from which the undersigned is authorized to draw.

Dated: April 24, 2016

Respectfully submitted,

By: /Mary J. Edwards/
Mary J. Edwards
Registration No.: 55,140
GILEAD SCIENCES, INC.
Correspondence Customer Number: 25000
(650) 522-1816
Attorney For Applicant

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/346,335	Filing Date 11/08/2016	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 = *		X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 = *		X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT		(Column 1)		(Column 2)	(Column 3)	RATE ($)	ADDITIONAL FEE ($)
	04/24/2018	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		
	Total (37 CFR 1.16(i))	· 22	Minus	** 46	= 0	X $100 =	0
	Independent (37 CFR 1.16(h))	· 1	Minus	***12	= 0	X $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1)		(Column 2)	(Column 3)	RATE ($)	ADDITIONAL FEE ($)
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		
	Total (37 CFR 1.16(i))	·	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	·	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
CAROLYN THOMAS

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C	1307

25000 7590 05/11/2018

GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CALIFORNIA 94404
UNITED STATES OF AMERICA

EXAMINER
WORSHAM, JESSICA N

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
05/11/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPDocketing@gilead.com
IPUS2@gilead.com

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 15/346,335	Applicant(s) Collman et al.	
	Examiner JESSICA WORSHAM	Art Unit 1615	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 24 April 2018.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-5,26-27 and 52-54 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-3 is/are rejected.

8) ☑ Claim(s) 4-5,26-27 and 52-54 is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 10/6/17.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1494 of 1915

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Detailed Action

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 6 October 2017 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner. See attached copy of PTO-1449.

Response to Restriction

2. Applicant's election of Group I (claims 1-5, 26, 27, and 52-54) in the reply filed on 24 April 2018 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.01(a)).

Status of Application

3. The instant application was filed 8 November 2016 with provisional 62/399.999 filed 26 September 2016 and 62/253,042 filed 9 November 2015. Claims 1-5, 26-27, and 52-54 are currently pending. Claims 6-25 and 28-51 have been cancelled. Claims 52-54 are newly added. Claims 1-5 and 26-27 have been amended. Claims 1-5, 26-27, and 52-54 are examined on the merits within.

Claim Objections

4. Claims 4-5, 26-27, and 52-54 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only, and/or, cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 4-5, 26-27, and 52-54 have not been further treated on the merits.

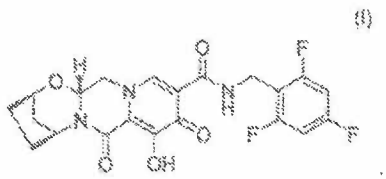
Claim Rejections – 35 U.S.C. 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

6. Claim(s) 1-3 is/are rejected under 35 U.S.C. 102(a)(2) as being anticipated by Carra et al. (WO2015/196116).

Carra et al. disclose the compound of Formula 1:



(I)

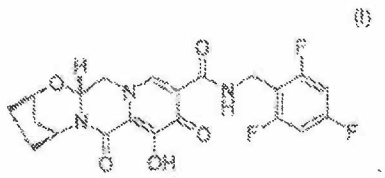
Carra et al. disclose the compound of Formula I in a composition comprising one to three additional therapeutic agents wherein these agents are anti-HIV drugs. See claim 14. The composition further comprises tenofovir alafenamide and emtricitabine. See claim 18. The composition is in the form of a tablet. See claim 21. The compound of Formula II, which is the

sodium salt of the compound of Formula 1, is present in amounts of 25-100 mg. See paragraph [0058]. Tenofovir alafenamide is present in 5-30 mg and emtricitabine is present in 200 mg. See paragraph [0096].

Thus the instant claims are anticipated by Carra et al.

7. Claim(s) 1-3 is/are rejected under 35 U.S.C. 102(a)(2) as being anticipated by Carra et al. (U.S. Patent Application Publication No. 2016/0016973).

Carra et al. disclose the compound of Formula 1:



Carra et al. disclose the compound of Formula 1 in a composition comprising one to three additional therapeutic agents wherein these agents are anti-HIV drugs. See claim 14. The composition further comprises tenofovir alafenamide and emtricitabine. See claim 18. The composition is in the form of a tablet. See claim 21. The compound of Formula II, which is the sodium salt of the compound of Formula 1, is present in amounts of 25-100 mg. See paragraph [0063]. Tenofovir alafenamide is present in 5-30 mg and emtricitabine is present in 200 mg. See paragraph [0139].

Thus the instant claims are anticipated by Carra et al.

Conclusion

8. No claims are allowed at this time.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to JESSICA WORSHAM whose telephone number is (571)270-7434. The examiner can normally be reached on Monday-Friday (8-5).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Wax can be reached on 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JESSICA N WORSHAM/
Primary Examiner, Art Unit 1615

Notice of References Cited	Application/Control No. 15/346,335	Applicant(s)/Patent Under Reexamination Collman et al.	
	Examiner JESSICA WORSHAM	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20160016973-A1	01-2016	Carra; Ernest A.	C07D498/18	514/81
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1499 of 1915

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Inventor Search: EAST, PALM	05/03/2018	JW
EAST: See attached	05/03/2018	JW
SciFinder: See attached	05/03/2018	JW

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

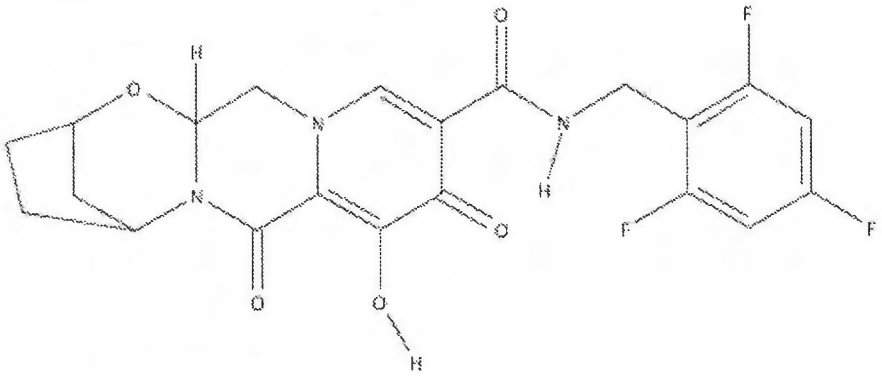
/JESSICA N WORSHAM/ Primary Examiner, Art Unit 1615	

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1500 of 1915

Task History

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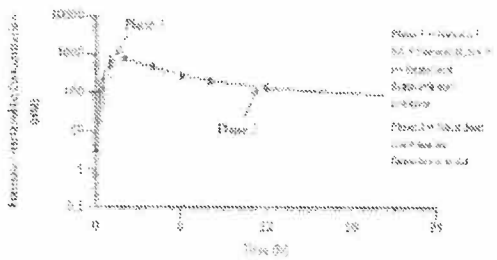
Answer Type: *Substances*
Result Count: *137*

Retrieve reference information in 1 substance (ID 2)

From ID: 1
Answer Type: *References*
Result Count: *23*

1. Therapeutic compositions for treatment of human immunodeficiency virus

By Bischofberger, Norbert W.; Cheng, Andrew; Lee, William A.; Sperger, Diana; Tijerina, Monica
From U.S. Pat. Appl. Publ. (2018), US 20180085387 A1 20180329, Language: English, Database: CAPLUS



~0 Citings

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2. Combination comprising tenofovir alafenamide, bictegravir and 3TC

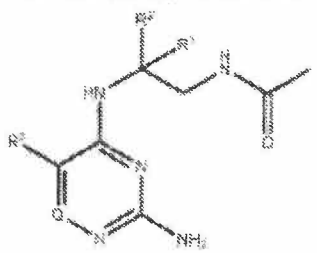
By Aboud, Michael
From PCT Int. Appl. (2018), WO 2018051250 A1 20180322, Language: English, Database: CAPLUS

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3. Fused pyrimidinamines and related compounds as toll-like receptor modulators and their preparation

By Chin, Gregory; Mackman, Richard L.; Mish, Michael R.; Zablocki, Jeff
From PCT Int. Appl. (2018), WO 2018045144 A1 20180308, Language: English, Database: CAPLUS



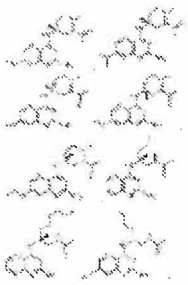
Formula I

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4. Preparation of diaminopyridopyrimidine derivatives for use as toll like receptor modulators

By Chin, Gregory; Mackman, Richard L.; Mish, Michael R.; Zablocki, Jeff
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5. Bictegravir combinations for treating HIV

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6. Combinations and uses and treatments thereof

By Johns, Brian Alvin
From PCT Int. Appl. (2018), WO 2018044838 A1 20180308, Language: English, Database: CAPLUS

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By Graupe, Michael; Henry, Steven J.; Link, John O.; Rowe, Charles William; Saito, Roland D.; Schroeder, Scott D.; Stefanidis, Dimitrios; Tse, Winston C.; Zhang, Jennifer R.
From PCT Int. Appl. (2018), WO 2018035359 A1 20180222, Language: English, Database: CAPLUS

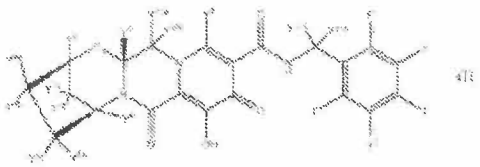


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By Tung, Roger D.
From PCT Int. Appl. (2018), WO 2018005328 A1 20180104, Language: English, Database: CAPLUS



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9. Combinations for treating HIV infections

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11. Role of tenofovir alafenamide (TAF) in the treatment and prophylaxis of HIV and HBV infections

By De Clercq, Erik
From Biochemical Pharmacology (Amsterdam, Netherlands) (2017), Ahead of Print. Language: English, Database: CAPLUS, DOI:10.1016/j.bcp.2017.11.023

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12. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial

By Sax, Paul E.; Pozniak, Anton; Montes, M. Luisa; Koenig, Ellen; De Jesus, Edwin; Stellbrink, Hans-Jurgen; Antinori, Andrea; Workowski, Kimberly; Slim, Jihad; Reynes, Jacques; et al
From Lancet (2017), 390(10107), 2073-2082. Language: English, Database: CAPLUS, DOI:10.1016/S0140-6736(17)32340-1

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By Gallant, Joel; Lazzarin, Adriano; Mills, Anthony; Orkin, Chloe; Podzamczer, Daniel; Tebas, Pablo; Girard, Pierre-Marie; Brar, Indira; Daar, Eric S.; Wohl, David; et al
From Lancet (2017), 390(10107), 2063-2072. Language: English, Database: CAPLUS, DOI:10.1016/S0140-6736(17)32299-7

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14. Pharmaceutical compositions comprising an anti-retroviral drug and a pharmacokinetic enhancer

By Malhotra, Geena; Joshi, Kalpana; Raut, Preeti
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15. Investigational HIV integrase inhibitors in phase I and phase II clinical trials

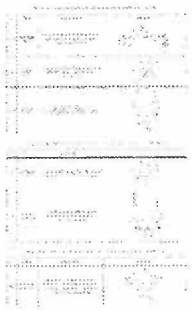
By Han, Yingshan; Mesplede, Thibault; Wainberg, Mark A.
From Expert Opinion on Investigational Drugs (2017), 26(11), 1207-1213. Language: English, Database: CAPLUS, DOI:10.1080/13543784.2017.1378643

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16. Preparation of acyclic nucleotide analogs as antiviral agents

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17. Recent Advances in Antiretroviral Agents: Potent Integrase Inhibitors

By Psichogiou, Mina; Poulakou, Garyphalia; Basoulis, Dimitrios; Paraskevis, Dimitrios; Markogiannakis, Antonios; Daikos, George L.
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18. Therapeutic compositions containing polycyclic-carbamoylpyridone compound, tenofovir alafenamide, and emtricitabine for treatment of human immunodeficiency virus

By Hong, Lei; Collman, Benjamin Micah
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By Tsiang, Manuel; Jones, Gregg S.; Goldsmith, Joshua; Mulato, Andrew; Hansen, Derek; Kan, Elaine; Tsai, Luong; Bam, Rujuta A.; Stepan, George; Stray, Kirsten M.; et al
From Antimicrobial Agents and Chemotherapy (2016), 60(12), 7086-7097. Language: English, Database: CAPLUS, DOI:10.1128/AAC.01474-16

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20. Preparation of toll-like receptor modulating 4,6-diamino-pyrido[3,2-d]pyrimidines and use in mono- and combination therapy

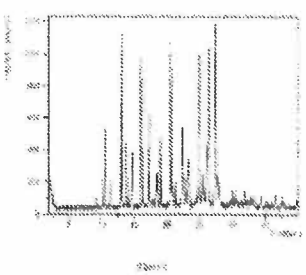
By Aktoudianakis, Evangelos; Chin, Gregory; Mackman, Richard L.; Metobo, Samuel E.; Mish, Michael R.; Pyun, Hyung-Jung; Zablocki, Jeff
From PCT Int. Appl. (2016), WO 2016141092 A1 20160909. Language: English, Database: CAPLUS

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21. Crystalline forms of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanpyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide

By Carra, Ernest A.; Chen, Irene; Keaton, Katie Ann; Zia, Vahid
From PCT Int. Appl. (2015), WO 2015196137 A1 20151223, Language: English, Database: CAPLUS

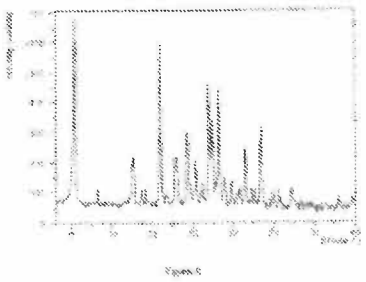


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By Carra, Ernest A.; Chen, Irene; Zia, Vahid
From PCT Int. Appl. (2015), WO 2015198116 A1 20151223. Language: English, Database: CAPLUS

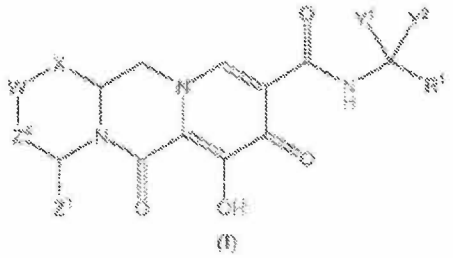


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23. Preparation of polycyclic-carbamoylpyridone compounds and their pharmaceutical use

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	539	((("GILEAD") near3 ("SCIENCES") near3 ("INC"))).AS,AANM.	USPAT	OR	OFF	2018/05/03 07:06
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S3	62	((("Hong") near3 ("Lei"))).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/05/03 07:06
S4	9	((("Koziara") near3 ("Joanna") near3 ("M"))).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/05/03 07:06
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S17	6	"9216996".pn.	US-PGPUB; USPAT; USOCR;	OR	OFF	2018/05/03 08:47

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S29	3	"20150150810"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/05/03 08:48
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S36	2	"20140349971"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/05/03 08:49
S37	2	"20080200435"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/05/03 08:49
S38	2	"20150283135"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/05/03 08:49
S39	4	"20140142070"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/05/03 08:49
S40	2	"8598185".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/05/03 08:49
S41	3	"9018192".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/05/03 08:49
S42	2	"9545414".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/05/03 08:49
S43	3	"20170079999"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/05/03 08:49
S44	6	"20160016973"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2018/05/03 10:26
S45	304	((("GILEAD") near3 ("SCIENCES") near3 ("INC"))).AS,AANM. and HIV	USPAT	OR	OFF	2018/05/03 10:33
S46	0	"20140221355"	USPAT	OR	OFF	2018/05/03 10:40
S47	1	"20140221355"	US-PGPUB;	OR	OFF	2018/05/03

			USPAT			10:40	

5/ 4/ 2018 7:14:40 AM
C:\ Users\ jworsham\ Documents\ EAST\ Workspaces\ 15346335.wsp

Bibliographic Data

Application No: 15/346,335

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /JESSICA WORSHAM/ Examiner's Signature | Initials

Title: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/08/2016	424	1615	1147.P2C
RULE			

APPLICANTS

Gilead Sciences, Inc., Foster City, CA.

INVENTORS

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Lei Hong Cupertino, CA, UNITED STATES

Joanna M. Koziara Foster City, CA, UNITED STATES

CONTINUING DATA

This application has PRO of 62399999 09/26/2016

This application has PRO of 62253042 11/09/2015

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

11/15/2016

STATE OR COUNTRY

UNITED STATES

ADDRESS

GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404
UNITED STATES

FILING FEE RECEIVED

$1,740

PTO/SB/08a (07-09)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	Jessica N. Worsham
Attorney Docket Number	1147.PC

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US-8,592,397	11-26-2013	Dahl et al.	
	AB	US-8,716,264	05-06-2014	Dahl et al.	
	AC	US-9,216,996	12-22-2015	Jin et al.	
	AD	US-9,457,036	10-04-2016	Dahl et al.	
	AE	US-9,663,528	05-30-2017	Desai et al.	
	AF	US-9,682,084	06-20-2017	Carra et al.	
	AG	US-9,708,342	07-18-2017	Carra et al.	
	AH	US-9,732,092	08-15-2017	Jin et al.	
	AI	US-2007/0219243-A1	09-20-2007	Kearney et al.	
	AJ	US-2010/0285122-A1	11-11-2010	Oliyai et al.	
	AK	US-2013/0243857-A1	09-19-2013	Oliyai et al.	
	AL	US-2014/0213556-A1	07-31-2014	DAHL et al.	
	AM	US-2014/0221355-A1	08-07-2014	LAZERWITH et al.	
	AN	US-2015/0111856-A1	04-23-2015	Dahl et al.	
	AO	US-2015/0150810-A1	06-04-2015	OLIYAI et al.	
	AP	US-2016/0194335-A1	07-07-2016	Jin et al.	
	AQ	US-2017/0027967-A1	02-02-2017	Koziara et al.	
	AR	US-2017/0114074-A1	04-27-2017	Jin et al.	
	AS	US-2017/0197985-A1	07-13-2017	Carra et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA	WO-2004/024078-A2	03-25-2004	Merck & Co., Inc.		
	BB	WO-2006/030807-A1	03-23-2006	Shionogi & Co., Ltd		
	BC	WO-2006/116764-A1	11-02-2006	Shionogi & Co., Ltd		
	BD	WO-2015/039348-A1	03-26-2015	Merck Sharp & Dohme		
	BE	WO-2014/100323-A1	06-26-2014	Gilead Sciences, Inc		
	BF	WO-2015/196137-A1	12-23-2015	Gilead Sciences, Inc		

Examiner Signature	/JESSICA WORSHAM/	Date Considered	05/04/2018

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: October 5, 2017 Signature: /Mary J. Edwards/ (Mary J. Edwards)

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PTO/SB/08a (07-09)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 4

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	Jessica N. Worsham
Attorney Docket Number	1147.PC

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AT	US-2017/0000807-A1	01-05-2017	Koziara et al.	
	AU	US-8,841,310	09-23-2014	Janssen R & D Ireland	
	AV	US-2014/0349971-A1	11-27-2014	Janssen R & D Ireland	
	AW	US-2008/0200435-A1	08-21-2008	Janssen R & D Ireland	
	AX	US-2015/0283135-A1	10-08-2015	Janssen R & D Ireland	
	AY	US-2014/0142070-A1	05-22-2014	Delaet et al.	
	AZ	US-8,598,185	12-03-2013	Dahl et al.	
	AA1	US-9,018,192	04-28-2015	Dahl et al.	
	AB1	US-9,545,414	01-17-2017	Dahl et al.	
	AC1	US-2017-0079999-A1	03-23-2017	DAHL et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BG	WO-2015/196116-A1	12-23-2015	Gilead Sciences, Inc.		
	BH	WO-2013/116720-A1	08-08-2013	Gilead Sciences, Inc		
	BI	WO-2015/022351-A1	02-19-2015	Ratiopharm Gmbh		

Examiner Signature	/JESSICA WORSHAM/	Date Considered	05/04/2018

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	3	of	4

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	Jessica N. Worsham
Attorney Docket Number	1147.PC

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Eron, Joe et al. (2016) "Retesting of suspected low-level HIV-1 viral load blips: A new paradigm to prevent extra clinic visits and unnecessary patient anxiety" Abstract, 10/28/2016 New Orleans	
	CB	Gallant Joel et al. (2016) Abstract "Novel INSTI GS-9883 10 Day Monotherapy in HIV-1 Infected Subjects " ASM2016	
	CC	Gallant, Joel et al. (2016) "Novel Integrase Strand Transfer Inhibitor Bictegravir 10 Day Monotherapy in HIV-1-Infected Patients" ASMMicrobe2016	
	CD	Jones, Gregg et al. (2016) Poster #413 "Bictegravir (GS-9883), a Novel HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Optimized In Vitro Resistance Profile"	
	CE	Lazerwith, Scott E. (2016) Poster #414 "Discovery of Bictegravir (GS-9883), a Novel, Unboosted, Once-Daily HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Improved Pharmacokinetics and In Vitro Resistance Profile"	
	CF	Lazerwith, Scott E. et al. Abstract "Discovery of GS-9883, an HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Improved Pharmacokinetics and In Vitro Resistance Profile "	
	CG	Moss et al. (2012) "Divalent metals and pH alter raltegravir disposition in vitro." American Society for Microbiology doi:10.1128/AAC.06407-11	
	CH	Patel, Parul et al. (2014) "Relative bioavailability of a paediatric granule formulation of the HIV intergrase inhibitor dolutegravir in healthy adult subjects." Antiviral Therapy (19):229-233	
	CI	Sax, Paul E. (2016) "Randomized Trial of Bictegravir or Dolutegravir with FTC/TAF for Initial HIV Therapy" CROI BIC 09/08/2016	
	CJ	Search Report - Intl Search Report - Written Opinion dated January 24, 2007 for PCT/US2016/060989	

Examiner Signature	/JESSICA WORSHAM/	Date Considered	05/04/2018

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[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 4 of 4

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Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	Jessica N. Worsham
Attorney Docket Number	1147.PC

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CK	Thomson Reuters Drug News (2011) "Gilead and Tibotec finalize agreement on single-tablet HIV regimen" http://drugnews.thomson-pharma.com/ddn/article.do?id=113441&source=Company Communication&section=AIDS#	
	CL	Tsiang, M. et al. "Antiviral Activity of GS-9883, a Potent Next Generation HIV-1 Integrase Strand Transfer Inhibitor" (ASMMicrobe20161)	
	CM	Tsiang, M. et al. "GS-9883, a Novel HIV-1 Integrase Strand Transfer Inhibitor (INSTI) with Optimized In Vitro Resistance Profile" (ASMMicrobe20162)	
	CN	Tsiang, M. et al. (2016) Poster #416 "Antiviral Activity of Bictegravir (GS-9883), a Potent Next Generation HIV-1 Integrase Strand Transfer Inhibitor"	
	CO	White, Kristen et al. (2016) "Potent Activity of Bictegravir (BIC; GS-9883), a Novel Unboosted; HIV-1 Integrase Strand Transfer Inhibitor (INSTI), Against Patient Isolates; with INSTI-Resistance" EU Workshop HIV Hepatitis;	
	CP	White, Kristen et al. (2016) Poster "The Integrase Strand Transfer Inhibitor Bictegravir has; a Long Integrase/DNA Dissociation Half-life" ;	
	CQ	White, Kristen et al. (2016) The Integrase Strand Transfer Inhibitor Bictegravir has a Long Integrase/DNA Dissociation Half-life	
	CR	White, Kritsten et al. (2017) "Bictegravir Dissociation Half-life from HIV-1 G140S+Q148H Integrase/DNA Complexes " CROI BIC	
	CS	Zhang et al. (2017) "Clinical Pharmacology of the HIV Integrase Strand Transfer Inhibitor Bictegravir " CROI BIC 09/26/2016	

Examiner Signature	/JESSICA WORSHAM/	Date Considered	05/04/2018

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[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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To: IPDocketing@gilead.com,IPUS2@gilead.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 25000

May 11, 2018 04:20:34 AM

Dear PAIR Customer:

GILEAD SCIENCES, INC
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FOSTER CITY, CA 94404
UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
15346335	CTNF	05/11/2018	1147.P2C
	892	05/11/2018	1147.P2C
	1449	05/11/2018	1147.P2C

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Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

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Dated: September 10, 2018 Signature: /David Castro/ (David Castro)

Docket No.: 1147.P2C (PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Benjamin Micah Collman et al.

Application No.: 15/346,335		Conf. No.:	1307
Filed:	November 8, 2016	Art Unit:	1615
For:	THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS	Examiner:	Jessica N. Worsham

AMENDMENT AND RESPONSE UNDER 37 CFR 1.111

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This communication is submitted in response to the Office Action dated May 11, 2018. This response is being filed via EFS-Web, along with payment for the Extension of Time Fee under 37 C.F.R. § 1.136(a).

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

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AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of the claims in the application:

1. (Currently Amended) A multilayer tablet comprising 50 mg of the compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof wherein the tablet has a total weight of less than about 1000 mg.

2. (Previously Presented) The tablet of claim 1, wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

3. (Previously Presented) The tablet of claim 1 or 2, wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I and 28 mg tenofovir alafenamide hemifumarate.

4. (Currently Amended) The tablet of ~~any one of claims 1-3~~ claim 3, wherein the tablet has a total weight of less than about 800 mg.

5. (Currently Amended) The tablet of ~~any one of claims 1-3~~ claim 3, wherein the tablet has a total weight of less than about 730 mg.

6-25 (Canceled)

26. (Currently Amended) The tablet of ~~any one of claims 1-5~~ claim 1 or 2, wherein the tablet contains less than about 15% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

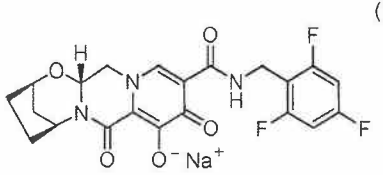
27. (Currently Amended) The tablet of ~~any one of claims 1-5~~ claim 1 or 2, wherein the tablet contains less than about 11% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

28-51 (Canceled)

52. (Currently Amended) The tablet of ~~any one of claims 1-5, 26, and 27~~ claim 1 or 2, wherein the tablet is a coated tablet.

53. (Currently Amended) The tablet of ~~any one of claims 1-5, 26, and 27~~ claim 3, comprising:

(II)



(i) a first layer including:

Ingredient	Mass (mg/tablet)
Compound of Formula II	52.5 (*equivalent to 50 mg of the Compound of Formula I*)
Microcrystalline cellulose	246.3
Croscarmellose sodium	19.4
Magnesium Stearate	4.9

(ii) a second layer including:

Ingredient	Mass (mg/tablet)
Emtricitabine	200

Tenofovir alafenamide hemifumarate	28 (*equivalent to 25 mg tenofovir alafenamide*)
Microcrystalline cellulose	113.2
Croscarmellose sodium	30.2
Magnesium Stearate	5.7

and (iii) a film coating.

54. (Canceled)

55. (New) The tablet of claim 3, wherein the first layer comprises 52 mg of the compound of Formula II:

(II)



and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

REMARKS

Claims 1-5, 26, 27, and 52-55 are currently pending. Claims 1, 4, 5, 26, 27, 52, and 53 are currently amended. Claim 54 is canceled without prejudice. New claim 55 has been added. Applicant believes the amendments add no new matter to the claims. Accordingly, upon entry, claims 1-5, 26, 27, 52, 53 and 55 are pending examination.

Claim 1 has been amended to recite "a multilayer tablet". Support for this amendment can be found in the specification as-filed, for example, at paragraphs [0055], [0056], and [0073] and in original claim 16. Claim 1 has been further amended to incorporate the limitations of claim 54, which has been canceled.

Claims 4, 5, and 53 have been amended to depend from claim 3.

Claims 26, 27, and 52 have been amended to depend from claim 1 or 2.

Exemplary support for new claim 55 can be found at paragraph [0057] of the specification as-filed.

Applicant expressly reserves the right to present claims drawn to any canceled subject matter in this or any other filed applications.

Applicant respectfully requests reconsideration of the application in view of the amendments and remarks made herein.

Co-pending Applications

Applicant submits the following US patent applications are related to the instant application:

Appl. No.	Status	Patent or Pub. No.
14/133,858	Granted	9,216,996
14/815,504	Granted	9,663,528
15/349,934	Granted	9,732,092
15/599,151	Granted	10,035,809
15/923,261	Pending	
16/017,371	Pending	
14/745,121	Granted	9,682,084
16/008,931	Pending	
14/744,915	Granted	9,708,342
15/624,166	Published	2018/0065986
15/639,833	Published	2018/0022757

Objections to the Claims

The Office has objected to claims 4-5, 26-27 and 52-54 as being in improper form. The dependency of claims 4-5, 26, 27, 52, and 53 has been revised and claim 54 has been canceled, rendering the objections moot.

Claim Rejections Under 35 U.S.C. § 102(a)(2)

Claims 1-3 have been rejected as being anticipated by Carra *et al.* (WO2015/196116) and Carra *et al.* (US Patent Application Publication No. 2016/0016973), hereinafter collectively "Carra *et al.*"

Applicant respectfully disagrees. Claims 1-3 are drawn to a fixed dose combination tablet comprising specific amounts of three components, including 50 mg of the compound of Formula I (bictegravir), and applicant has amended claim 1 to focus on a multilayer tablet having a total weight of less than about 1000 mg. The instantly claimed formulation has surprising pharmacokinetic benefits, as described in paragraphs [0317] and [0345] of the specification as-filed. For example, a bilayer tablet formulation of bictegravir, tenofovir alafenamide, and

emtricitabine results in approximately 30% higher total exposure of bictegravir compared to the corresponding total exposure achieved with a single agent formulation of bictegravir co-administered with a fixed dose combination of tenofovir alafenamide and emtricitabine (see paragraph [0317]).

Moreover, the instantly claimed formulation allows for a smaller tablet and, in turn, incurs reduced manufacturing costs. As stated in paragraph [0345] of the specification as-filed, despite containing one third less of the active ingredient (50 mg rather than 75 mg bictegravir), the instantly claimed formulation achieved exposure levels which still provide anti-HIV antiviral efficacy. Furthermore, despite the amount of bictegravir being lower in the instantly claimed formulation compared to a single agent formulation of bictegravir co-administered with a fixed dose combination of tenofovir alafenamide and emtricitabine, the exposure to tenofovir alafenamide and emtricitabine is similar for both treatments.

In view of the foregoing, withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicant requests reconsideration of this application in view of the present amendments. If the Office finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 07-1250, under Order No. 1147.P2C from which the undersigned is authorized to draw.

Dated: September 10, 2018

Respectfully submitted,

By: /Mary J. Edwards/
Mary J. Edwards
Registration No.: 55.140
GILEAD SCIENCES, INC.
Correspondence Customer Number: 25000
(650) 522-1816
Attorney For Applicant

Electronic Patent Application Fee Transmittal	
Application Number:	15346335
Filing Date:	08-Nov-2016
Title of Invention:	Therapeutic Compositions for Treatment of Human Immunodeficiency Virus
First Named Inventor/Applicant Name:	Benjamin Micah Collman
Filer:	Mary J. Edwards/David Castro
Attorney Docket Number:	1147.P2C
Filed as Large Entity	

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	1251	1	200	200
Miscellaneous:				
			Total in USD ($)	**200**

Electronic Acknowledgement Receipt	
EFS ID:	33675480
Application Number:	15346335
International Application Number:	
Confirmation Number:	1307
Title of Invention:	Therapeutic Compositions for Treatment of Human Immunodeficiency Virus
First Named Inventor/Applicant Name:	Benjamin Micah Collman
Customer Number:	25000
Filer:	Mary J. Edwards/David Castro
Filer Authorized By:	Mary J. Edwards
Attorney Docket Number:	1147.P2C
Receipt Date:	10-SEP-2018
Filing Date:	08-NOV-2016
Time Stamp:	16:31:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$200
RAM confirmation Number	091118INTEFSW00003786071250
Deposit Account	071250
Authorized User	David Castro
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees) 37 CFR 1.20 (Post Issuance fees) 37 CFR 1.21 (Miscellaneous fees and charges)					
File Listing:					
Document Number	**Document Description**	**File Name**	**File Size(Bytes)/ Message Digest**	**Multi Part /.zip**	**Pages (if appl.)**
1		1147P2C_2018-09-10_Response-to-Office-Action.PDF	64622 6f68f6192da4a35ac466feeeafc418921a2f15c4a	yes	7
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	4	
	Applicant Arguments/Remarks Made in an Amendment		5	7	
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30567 de13d2a22030dc5acf76db3049b6899172a517817	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	95189		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/346,335	Filing Date 11/08/2016	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 = *		X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 = *		X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 09/10/2018	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 20	Minus	** 46	= 0	X $100 =	0
Independent (37 CFR 1.16(h))	* 1	Minus	*** 12	= 0	X $460 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
MOLIKI MAY

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C	1307

25000 7590 12/21/2018

GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

EXAMINER
WORSHAM, JESSICA N

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
12/21/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPDocketing@gilead.com
IPUS2@gilead.com

Office Action Summary	Application No. 15/346,335	Applicant(s) Collman et al.	
	Examiner JESSICA WORSHAM	Art Unit 1615	AIA Status Yes

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 10 September 2018.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-5,26-27,52-53 and 55 is/are pending in the application.
5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-5,26-27,52-53 and 55 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Detailed Action

Status of Application

1. Applicants' arguments/remarks filed 10 September 2018 are acknowledged. Claims 1-5, 26-27, 52-53 and 55 are currently pending. Claims 6-25, 28-51, and 54 have been cancelled. Claim 55 is newly added. Claims 1, 4-5, 26-27, and 52-53 have been amended. Claims 1-5, 26-27, 52-53, and 55 are examined on the merits within.

Withdrawn Objections/Rejections

2. Applicants' arguments, see page 6, filed 10 September 2018, with respect to the claim objections have been fully considered and are persuasive. The objections of claims 4-5, 26-27, and 52-54 have been withdrawn in view of the claim amendments. The 35 U.S.C. 102(a)(2) rejections have been withdrawn in view of the claim amendments.

New Rejections

Claim Rejections – 35 U.S.C. 112, Second Paragraph or 112(b)

3. The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 53 and 55 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 53 recites the first and second layer in table form. Claims may contain tables either if necessary to conform to 35 U.S.C. 112 or if otherwise found to be desirable. See MPEP 2173.05(s). When such a patent is printed, however, the table will not be included as part of the claim, and instead the claim will contain a reference to the table number. Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." *Ex parte Fressola*, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted). In the instant case, there is a more practical way to define the invention without the use of a table. For example "a first layer including 52.5 mg of the compound of Formula II, 246.3 mg microcrystalline cellulose, 19.4 mg croscarmellose sodium, and 4.9 mg magnesium stearate…"

It is also noted that claim 53 recites 52.5 mg of the compound of Formula II. The compound of Formula II is the sodium salt of the compound of Formula I. This depends from claim 3 which recites that the tablet comprises 52 mg of the sodium salt of the compound of Formula I. Therefore, the amounts of claims 3 and 53 are conflicting. Clarification is requested.

Claim 55 recites "substantially free" which is not defined by the claim nor does the specification provide a standard for ascertaining the requisite metes and bounds, thus one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

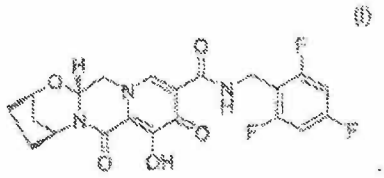
Claim Rejections – 35 U.S.C. 103

5. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 1-5, 26-27, 52-53, and 55 is/are rejected under 35 U.S.C. 103 as being unpatentable over Carra et al. (WO2015/196116) in view of Dahl et al. (U.S. Patent Application Publication No. 2007/0099902).

Carra et al. teach the compound of Formula 1:



Carra et al. teach the compound of Formula 1 in a composition comprising one to three additional therapeutic agents wherein these agents are anti-HIV drugs. See claim 14. The composition further comprises tenofovir alafenamide and emtricitabine. See claim 18. The composition is in the form of a tablet. See claim 21. The compound of Formula II, which is the sodium salt of the compound of Formula 1, is present in amounts of 25-100 mg. See paragraph [0058]. Tenofovir alafenamide is present in 5-30 mg and emtricitabine is present in 200 mg. See paragraph [0096]. Efavirenz is an HIV non-nucleoside or non-nucleotide inhibitor of reverse transcriptase that can be used as an additional therapeutic. See paragraph [0082]. The composition comprises

surfactants to facilitate dissolution of the compound of the invention. See paragraph [0066]. Table 3 shows that the tablets comprise 30% active ingredient, 56% microcrystalline cellulose, 13% croscarmellose sodium, and 1% magnesium stearate.

Carra et al. do not teach a multilayer tablet.

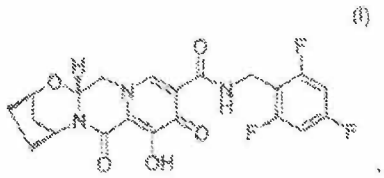
Dahl et al. teach a bilayer tablet of efavirenz, emtricitabine, and tenofovir. See paragraph [0050]. The unit dosage form comprises 1596.5 mg of ingredients per tablet. See Table 3. It is noted that efavirenz is present in 600 mg/tablet (see Table 1), emtricitabine is present in 200 mg/tablet and tenofovir is present in 300 mg/tablet (see Table 2). Typically the components of the dosage form are organized in multiple layers. See paragraph [0013]. The organization is so that tenofovir is not placed in destabilizing contact with the surfactant of the efavirenz component. See paragraph [0016]. The bilayer tablet is film coated. See paragraph [0050]. Dahl et al. teach 38.71% efavirenz combined with 11.52% microcrystalline cellulose, 2.48% hydroxypropylcellulose, 0.77% sodium lauryl sulfate, 3.87% croscarmellose sodium and 0.58% magnesium stearate in a first layer with 12.9% emtricitabine, 19.35% tenofovir, 5.77% microcrystalline cellulose, 3.1% crsocarmellose sodium and 0.94% magnesium stearate in a second layer. See tables 1 and 2.

It would have been obvious to one of ordinary skill in the art at the time the invention was filed to formulate the dosage form in a bilayer tablet to separate tenofovir from the compound of Carra et al. in order to prevent destabilizing contact of tenofovir with the surfactant. One would have been motivated, with a reasonable expectation of success, to provide a unit dosage form that is more easily administered while maintaining stability. It would have been well within the purview of the skilled artisan to coat the tablets because it is commonly known to provide coatings on pharmaceuticals to mask the taste of the active ingredients and/or provide a desired therapeutic

release profile. It would have been well within the purview of the skilled artisan to modify the amounts of ingredients and weight of the tablet to optimize the formulation to achieve the desired result, especially since the combination of ingredients are commonly known in similar formulations.

7. Claim(s) 1-5, 26-27, 52-53, and 55 is/are rejected under 35 U.S.C. 103 as being unpatentable over Carra et al. (U.S. Patent Application Publication No. 2016/0016973) in view of Dahl et al. (U.S. Patent Application Publication No. 2007/0099902).

Carra et al. teach the compound of Formula 1:



Carra et al. teach the compound of Formula 1 in a composition comprising one to three additional therapeutic agents wherein these agents are anti-HIV drugs. See claim 14. The composition further comprises tenofovir alafenamide and emtricitabine. See claim 18. The composition is in the form of a tablet. See claim 21. The compound of Formula II, which is the sodium salt of the compound of Formula 1, is present in amounts of 25-100 mg. See paragraph [0063]. Tenofovir alafenamide is present in 5-30 mg and emtricitabine is present in 200 mg. See paragraph [0139]. Efavirenz is an HIV non-nucleoside or non-nucleotide inhibitor of reverse transcriptase that can be used as an additional therapeutic. See paragraph [0087]. The composition comprises surfactants to facilitate dissolution of the compound of the invention. See paragraph [0071]. Table

3 shows that the tablets comprise 30% active ingredient, 56% microcrystalline cellulose, 13% croscarmellose sodium, and 1% magnesium stearate.

Carra et al. do not teach a multilayer tablet.

Dahl et al. teach a bilayer tablet of efavirenz, emtricitabine, and tenofovir. See paragraph [0050]. The unit dosage form comprises 1596.5 mg of ingredients per tablet. See Table 3. It is noted that efavirenz is present in 600 mg/tablet (see Table 1), emtricitabine is present in 200 mg/tablet and tenofovir is present in 300 mg/tablet (see Table 2). Typically the components of the dosage form are organized in multiple layers. See paragraph [0013]. The organization is so that tenofovir is not placed in destabilizing contact with the surfactant of the efavirenz component. See paragraph [0016]. The bilayer tablet is film coated. See paragraph [0050]. Dahl et al. teach 38.71% efavirenz combined with 11.52% microcrystalline cellulose, 2.48% hydroxypropylcellulose, 0.77% sodium lauryl sulfate, 3.87% croscarmellose sodium and 0.58% magnesium stearate in a first layer with 12.9% emtricitabine, 19.35% tenofovir, 5.77% microcrystalline cellulose, 3.1% crsocarmellose sodium and 0.94% magnesium stearate in a second layer. See tables 1 and 2.

It would have been obvious to one of ordinary skill in the art at the time the invention was filed to formulate the dosage form in a bilayer tablet to separate tenofovir from the compound of Carra et al. in order to prevent destabilizing contact of tenofovir with the surfactant. One would have been motivated, with a reasonable expectation of success, to provide a unit dosage form that is more easily administered while maintaining stability. It would have been well within the purview of the skilled artisan to coat the tablets because it is commonly known to provide coatings on pharmaceuticals to mask the taste of the active ingredients and/or provide a desired therapeutic release profile. It would have been well within the purview of the skilled artisan to modify the

amounts of ingredients and weight of the tablet to optimize the formulation to achieve the desired result, especially since the combination of ingredients are commonly known in similar formulations.

Response to Arguments

Applicants' arguments filed 10 September 2018 have been fully considered but they are not persuasive.

8. Applicants argued "The instantly claimed formulation has surprising pharmacokinetic benefits. The bilayer tablet formulation yields 30% higher total exposure of bictegravir compared to a single agent formulation of bictegravir co-administered with a fixed dose combination of tenofovir alafenamide and emtricitabine. The formulation allows for a smaller tablet, reducing manufacturing costs."

In response to applicants' arguments, the unexpected results of 30% higher total exposure occurred with the bilayer tablet F2, which comprises 78.7 mg of the compound of formula II, 247.8 mg microcrystalline cellulose, 21.2 mg croscarmellose sodium, and 5.3 mg magnesium stearate in one layer and 200 mg emtricitabine. 28.1 mg tenofovir, 113.1 mg microcrystalline cellulose, 30.2 mg croscarmellose sodium, and 5.7 mg magnesium stearate in a second layer. This does not correspond to claim 1, which is directed to 50 mg of the compound of Formula I. In addition, the specification shows a specific formulation wherein ingredients are in specified layers. Although claim 1 recites multilayer tablet, there is no mention of which ingredients are in which layers. Claims 53 and 55 are directed to more specific formulations, however the data provided is not commensurate in scope with the claims. therefore a side by side analysis cannot be conducted. In response to applicants' argument that the references fail to show certain features of applicant's

invention, it is noted that the features upon which applicant relies (i.e., smaller tablet) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Thus these rejections are maintained.

Conclusion

9. Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

10. No claims are allowed at this time.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to JESSICA WORSHAM whose telephone number is (571)270-7434. The examiner can normally be reached on Monday-Friday (8-5).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Wax can be reached on 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JESSICA WORSHAM/
Primary Examiner, Art Unit 1615

Notice of References Cited	Application/Control No. 15/346,335	Applicant(s)/Patent Under Reexamination Collman et al.	
	Examiner JESSICA WORSHAM	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20070099902-A1	05-2007	Dahl; Terrence C.	A61K9/2054	514/221
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
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	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 25000

Dec 21, 2018 03:46:05 AM

Dear PAIR Customer:

GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 25000 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

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Application	Document	Mailroom Date	Attorney Docket No.
15346335	CTFR	12/21/2018	1147.P2C
	892	12/21/2018	1147.P2C

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

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Thank you for prompt attention to this notice,

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Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).
   - a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
     - i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
     - ii. ☐ Other _____
   - b. ☒ Enclosed
     - i. ☒ Amendment/Reply
     - ii. ☐ Affidavit(s)/ Declaration(s)
     - iii. ☐ Information Disclosure Statement (IDS)
     - iv. ☐ Other _____

2. Miscellaneous
   - a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
   - b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
   - a. ☒ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 07-1250 .
     - i. ☒ RCE fee required under 37 CFR 1.17(e)
     - ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)
     - iii. ☐ Other _____
   - b. ☐ Check in the amount of $ _____ enclosed
   - c. ☐ Payment by credit card (Form PTO-2038 enclosed)
   - d. ☒ Payment by EFS-Web

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Donna Johnson Gressler/	Date	March 20, 2019
Name (Print/Type)	Donna Johnson Gressler	Registration No.	45,544

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office (USPTO), deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the USPTO on the date shown below.

Signature			
Name (Print/Type)		Date	

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: March 20, 2019 Electronic Signature for David Castro: /David Castro/

1042154.1

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: March 20, 2019 Signature: /David Castro/ (David Castro)

Docket No.: 1147.P2C (PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Benjamin Micah Collman et al.

Application No.: 15/346,335		Conf. No.:	1307
Filed:	November 8, 2016	Art Unit:	1615
For:	THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS	Examiner:	Jessica N. Worsham

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION UNDER 37 CFR 1.111

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This communication is submitted in response to the Final Office Action dated December 21, 2018.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

Electronic Patent Application Fee Transmittal					
Application Number:	15346335				
Filing Date:	08-Nov-2016				
Title of Invention:	Therapeutic Compositions for Treatment of Human Immunodeficiency Virus				
First Named Inventor/Applicant Name:	Benjamin Micah Collman				
Filer:	Donna Johnson Gressler/David Castro				
Attorney Docket Number:	1147.P2C				
Filed as Large Entity					
Filing Fees for Utility under 35 USC 111(a)					
Description		**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:					
Pages:					
Claims:					
Miscellaneous-Filing:					
Petition:					
Patent-Appeals-and-Interference:					
Post-Allowance-and-Post-Issuance:					
Extension-of-Time:					

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
RCE- 1ST REQUEST	1801	1	1300	1300
		Total in USD ($)		**1300**

Electronic Acknowledgement Receipt	
EFS ID:	35483329
Application Number:	15346335
International Application Number:	
Confirmation Number:	1307
Title of Invention:	Therapeutic Compositions for Treatment of Human Immunodeficiency Virus
First Named Inventor/Applicant Name:	Benjamin Micah Collman
Customer Number:	25000
Filer:	Donna Johnson Gressler/David Castro
Filer Authorized By:	Donna Johnson Gressler
Attorney Docket Number:	1147.P2C
Receipt Date:	20-MAR-2019
Filing Date:	08-NOV-2016
Time Stamp:	17:11:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1300
RAM confirmation Number	032119INTEFSW00004194071250
Deposit Account	071250
Authorized User	David Castro
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	1147P2C_2019-03-20_RCE.pdf	39325 873141ece196d3b0f26899ec0d0f2980dc7a a0b0	no	1
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2		1147P2C_2019-03-20_Response-to-FOA.pdf	76256 c2bbbf62a9cea2b0f0c8709dfdf677a15a5f60c 0ba	yes	9
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Applicant Arguments/Remarks Made in an Amendment		9	9	
	Claims		2	8	
	Amendment Submitted/Entered with Filing of CPA/RCE		1	1	
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30558 c0cfa572159f4bac56e18f2ac9159a23fec06 ace	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	146139		