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Once-Daily Single-Tablet Regimens: A Long and Winding Road to Excellence in Antiretroviral Treatment

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Abstract

Once-daily single-tablet regimens represent the paramount simplification of antiretroviral treatment achieved so far. They include drugs with favorable pharmacokinetics that allow once-daily administration, that do not need dose adjustments, have no additional toxicities, and do not require dissimilar intake conditions. Co-formulated efavirenz/tenofovir disoproxil fumarate/emtricitabine has been a gold standard of initial therapy since its approval in 2006. Galenic research and industry patent agreements may allow availability of single-tablet regimens with HIV-1 nonnucleoside reverse transcriptase inhibitors (efavirenz or rilpivirine), integrase inhibitors (cobicistat-boosted elvitegravir or dolutegravir), and protease inhibitors (cobicistat-boosted darunavir), combined with either tenofovir disoproxil fumarate/emtricitabine or abacavir/lamivudine. The introduction of the new phamacoenhancer cobicistat as a potential substitution for ritonavir and the investigational agent GS-7340, with one-tenth the tenofovir mass, is a breakthrough in antiretroviral drug development. Many HIV-1-infected patients who are treatment-naive or treatment-experienced with susceptible virus will potentially have more options to reduce pill burden and optimize dosage schedules with one pill once-daily regimens. **(AIDS Rev. 2012;14:168-78)**

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Key words

Antiretroviral agents. Antiretroviral therapy. Highly active. Drug therapy. Combination. HIV infection.

Introduction

HIV-1 infection entails lifelong antiretroviral treatment (ART), thereby challenging a patient's continued adherence. Subjects with low adherence are at an increased risk of virologic failure, disease progression, and death[1-4]. Continued simplification of ART during the past decade has achieved increasing reductions in pill burden, daily dosages, and less short- and long-term toxicities, ultimately facilitating treatment adherence[5-7]. It has also been associated with reduced rates of treatment failure and resistance selection[8-10].

Fixed-dose combinations have been pivotal in reducing the risk of treatment errors and selective non-adherence[11,12]. Except for cases where dose adjustments are required, fixed-dose combinations are recommended for treatment of HIV-1 infection when the agents included in the co-formulation are drugs of choice[10,13,14]. A single-tablet regimen (STR) co-formulation for once-daily dosing is the highest level of ART simplification achieved so far. In 2006 the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) in 2007, granted marketing authorization for a tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate (EFV/FTC/TDF), the first STR in the history of HIV treatment. It has been a preferred initial treatment in all guidelines since then[10,13,15]. Its use has been associated with significantly higher adherence, regimen persistence, and viral suppression rates, in addition to lower risks of

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hospitalization, both in the challenging homeless and marginally housed people, as well as in US Medicaid enrollees or the US LifeLink database[16-18]. Finally, patients on a STR had significantly lower healthcare costs (17% reduction) compared to patients receiving a two-or-more tablet per day regimen, although patients were not randomized and unmeasured confounding factors might have influenced outcomes[16].

The approval in 2011 of a second STR containing rilpivirine (RPV) plus TDF/FTC and submissions to the Health Authorities in 2012 of a third STR containing elvitegravir/cobicistat (EVG/COBI) plus TDF/FTC significantly expand the possibilities of administering complete ART as a once-daily STR.

This article reviews the efficacy and tolerability of STR, either commercially available or in the advanced pipeline.

Efavirenz/tenofovir disoproxil fumarate/emtricitabine

The combination of TDF plus FTC has been a preferred nucleoside reverse transcriptase inhibitor (NRTI) regimen since 2003 and has been studied with many different combinations[10,13,14]. Its efficacy has never been surpassed in any clinical trial. Not only has TDF plus FTC shown non-inferior or superior virologic efficacy compared to abacavir (ABC) plus lamivudine (3TC)[19-23], but it has also shown superior virologic efficacy compared to zidovudine plus 3TC[24,25] and to stavudine plus 3TC[26]. Furthermore, co-formulated TDF/FTC has demonstrated potent virologic activity in combination with all other components of preferred regimens[27-29] and is available in as a once-daily STR with EFV (Table 1).

Table 1. Plasma and intracellular elimination half-lives ($t_{1/2}$) of antiretroviral components of once-daily single-tablet antiretroviral regimens currently approved or in late-stage development[10]

Drug	Plasma $t_{1/2}$	Intracellular $t_{1/2}$
Tenofovir	17 h	> 60 h*
Emtricitabine	8.2-10 h	39 h*
Abacavir	1.5 h	12-26 h
Lamivudine	5-7 h	16-22 h
GS 7340	6.5 h†	> 60 h‡
Efavirenz	40-55 h	–
Rilpivirine	50 h	–
Elvitegravir	9.15 h (with COBI 150 mg)[60] 11.2 h (with RTV 100 mg)[60]	–
Dolutegravir	12-15 h[76,78]	–
Darunavir	10 h (with COBI 150 mg)§[79] 15 h (with RTV 100 mg)	–

$t_{1/2}$: half life; COBI: cobicistat; RTV: ritonavir; h: hours.
*Terminal $t_{1/2}$ of tenofovir diphosphate: 164 hours; terminal $t_{1/2}$ of emtricitabine triphosphate: 39 hours[83].
†Result seen in macaques; the shorter $t_{1/2}$ seen with GS 7340 is due to a significantly higher initial C_{max}, albeit subsequent kinetics are pretty similar to those obtained with tenofovir disoproxil fumarate[84].
‡The administration of GS 7340 results in an increased accumulation of parent tenofovir, up to 7-20 times in lymphatic tissues and PBMC, compared to tenofovir disoproxil fumarate[74,85]. GS 7340 has a $t_{1/2}$ of 90 minutes in human plasma at 37°C[74].
§Data calculated with sampling done only 24 hours post-dose, instead of 72 hours; using this method, ritonavir-boosted darunavir should have a terminal $t_{1/2}$ of 12 hours.
Adapted from Thomas Kakuda (Clinical Pharmacology, Infectious Diseases & Vaccines, Janssen), personal communication.

Nonnucleoside reverse transcriptase inhibitor (NNRTI) recommendations have remained unchanged since EFV was added to the preferred list in late 1998. It has been the gold standard NNRTI since then, and with the approval in 2006 of the first STR, EFV/TDF/FTC has been a preferred regimen in all guidelines[10,13,14]. In some guidelines, EFV has been the only first-line third component in all patients for some years[30]. This recommendation was based on its efficacy, durability, toxicity profile, convenience, and cost, while boosted protease inhibitors (PI) should be reserved for specific groups of patients. With similar safety and efficacy, its availability as a STR drives its selection for many patients, making it the simplest and least expensive regimen on the preferred list[31]. Efavirenz, either combined separately with two NRTI or co-formulated in the STR, has not been surpassed for efficacy in any clinical trial so far. It has demonstrated non-inferior efficacy against atazanavir/ritonavir (ATV/r), nevirapine (NVP), maraviroc, raltegravir (RAL), rilpivirine (RPV), elvitegravir (EVG), and dolutegravir (DTG) in treatment-naive subjects[19,28,32-38], as well as superiority against indinavir, nelfinavir, and ritonavir-boosted lopinavir[39-42]. There are no randomized controlled trials directly comparing EFV and darunavir/r (DRV/r). The efficacy of EFV is particularly preserved in subjects with a high baseline viral load or in subjects with very advanced immune suppression[39,40,43-45].

A major disadvantage of an EFV-based regimen is the low genetic barrier to resistance, since one mutation can render resistance to both EFV and NVP. In addition, resistance selection to both NNRTI and NRTI is common in virologic failures, with variable degrees

of impact on etravirine activity[46]. The main adverse effects of EFV are rash and central nervous system (CNS) effects, such as somnolence, dizziness, and abnormal dreams, all of which are usually transient and manageable in many patients. However, recent trials have shown that these adverse events may persist at 48 weeks in up to 15-20% of EFV-treated subjects[28,32,33].

Efavirenz may not be the preferred option for patients with a current or past history of significant mental health problems or patients taking methadone, and should not be used in patients with transmitted NNRTI resistance or when baseline genotypic resistance testing is unavailable[10,13,14]. Efavirenz should also be avoided in women of reproductive potential not using effective and consistent contraception and during pregnancy. Most of the drawbacks of EFV can be overcome or avoided, and the advantages outweigh the disadvantages in many patients. However, approximately 20% of all individuals commencing EFV/TDF/FTC need to switch therapy at 48 weeks in clinical practice, often for adverse events[47], verifying the need for alternative STR options.

Rilpivirine/tenofovir disoproxil fumarate/emtricitabine

Rilpivirine is a diarylpyrimidine NNRTI active against wild-type and some NNRTI-resistant isolates. It gained FDA and EMA approval in 2011 for treatment-naive adults as a single tablet or co-formulated in a STR with TDF/FTC. The bioavailability of RPV is pH dependent. Co-administration with omeprazole significantly reduced the steady state exposure of RPV, with a 40% reduction in the area under the concentration-time curve (AUC_{24h}), thus preventing co-administration[48]. Under fasting conditions, the maximum concentration (C_{max}) of RPV decreased by 46% and the AUC decreased by 43%[49]. As a consequence, it must be taken with a standard or high-fat meal.

In a large phase IIb dose-ranging study, RPV (TMC278-C204) demonstrated potent and sustained efficacy comparable to EFV in treatment-naive subjects over 96 weeks[50]. No RPV dose-response relationship for efficacy was observed in this trial (25, 75, or 150 mg once-daily). Thus, given that doses of RPV 75 mg once-daily and 300 mg once-daily prolonged the QTc interval of the electrocardiogram in healthy subjects, the 25 mg dose was chosen[51].

Two twin, double-blind, double-dummy phase III trials evaluated the efficacy of RPV 25 mg once daily compared to EFV, each combined with TDF/FTC (ECHO)[32] or any NRTI co-formulation (THRIVE; AZT/3TC, ABC/3TC, or TDF/FTC)[37], with approximately 340 patients in each arm and 686 total subjects treated with RPV. In the ECHO trial, 83% of patients with either RPV or EFV had a confirmed virologic response at 48 weeks (viral load < 50 copies/ml, ITT-TLOVR algorithm) with a –0.4 difference (95% CI: –5.9 to 5.2), confirming non-inferiority with a 12% margin (primary endpoint). The THRIVE trial had similar results with 86 and 82% efficacy rates, a difference of 3.5% (95% CI: –1.7 to 8.8). Non-inferiority was also demonstrated in the pooled analysis of both trials[52]. Increases in CD4 cell counts were similar with RPV and EFV. Virologic response was similar for each of the NRTI regimens, albeit only 35 (10%) subjects received RPV together with ABC/3TC in the THRIVE trial. Efficacy was similar by race and gender. The higher rates of virologic failure observed in the RPV arm were counterbalanced by the lower rates of discontinuations due to adverse events[32,37]. Grade 2-4 treatment-related adverse events were less common with RPV (16%) than with EFV (31%; $p < 0.0001$), including rash and dizziness ($p < 0.0001$ for both). Discontinuation due to adverse events was also more common with EFV (8%) than with RPV (2%). In the pooled analysis, EFV showed higher increases in total, HDL, and LDL cholesterol, as well as triglycerides ($p < 0.0001$ for all), with no differences between groups in the total/HDL cholesterol ratio at 96 weeks[52]. Limb fat changes and bone mineral density (DEXA Substudy) at week 96 in the pooled analysis showed no differences between RPV and EFV[53].

In the pooled analysis, RPV-treated subjects showed higher rates of virologic failure at 48 weeks vs. EFV-treated subjects: 11 vs. 5%, respectively, both as never-suppressed or rebounders[32,37,52]. Rilpivirine failures occurred mostly in subjects with baseline viral load > 100,000 copies/ml. The efficacy of RPV dropped from 90% in subjects with baseline viral load < 100,000 copies/ml to 77% in subjects with viral load > 100,000 copies/ml, while EFV maintained similar efficacy in both groups (84 and 81%, respectively). In this subset of patients, RPV failures occurred predominantly in subjects with suboptimal adherence[54]. Even though RPV demonstrated non-inferiority in the subset of patients with high baseline viral load in the pooled analysis (77 vs. 81%; treatment difference –3.6; 95% CI: –9.8, 2.5), resistance was frequently selected in subjects failing RPV, and these failures with resistance selection were overrepresented among subjects with higher baseline viral load[54]. Actually, the FDA sought a sensitivity regression tree analysis to determine if 100,000 copies/ml

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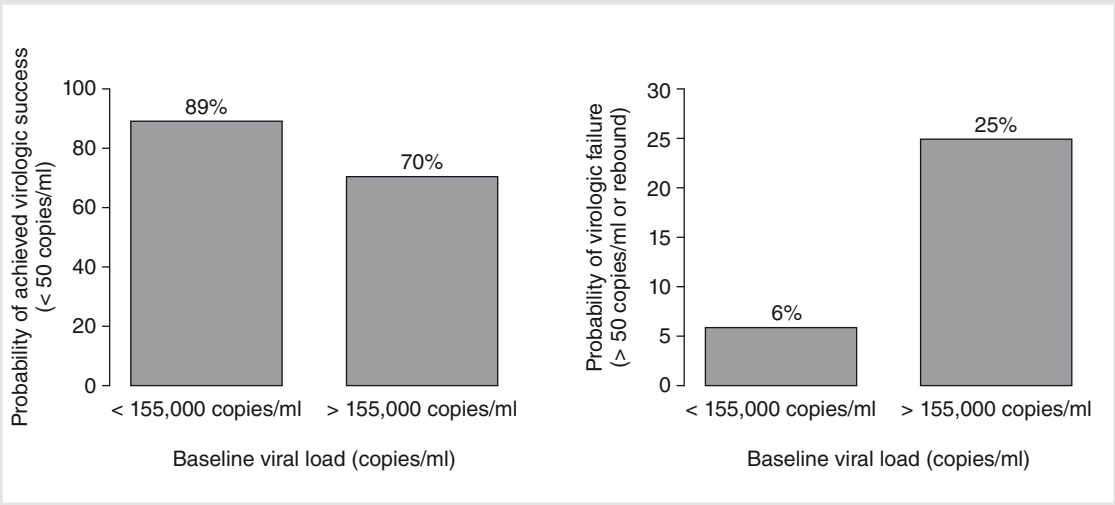

Figure 1. A FDA-sought regression tree analysis identified a cutoff point for rilpivirine virologic success (left) or virologic failure (right) based on baseline viral load in the ECHO and THRIVE studies. Based on this cutoff point, 89% (398/446) of patients with baseline viral load < 155,000 copies/ml achieved virologic success, compared to 72% (164/229) of patients with baseline viral load > 155,000 copies/ml. Similarly, 6% (25/446) of patients with baseline viral load < 155,000 copies/ml had virologic failure compared to 24% (55/229) of patients with baseline viral load > 155,000 copies/ml[32,37,55].

was indeed an accurate representation of the inflection point separating virologic successes from non-successes. This analysis identified 155,000 copies/ml as the baseline viral load cutoff point associated with the greatest change between groups for virologic success and failure (Fig. 1)[55]. Subjects with high and low viral load selected NNRTI resistance mutations at failure with RPV in 72 and 38% of the cases, respectively, and with EFV 63 and 42%, respectively. The NRTI resistance rates were 76 and 44%, respectively, in the RPV arm, and 44 and 17%, respectively, in the EFV arm. Therefore, selection of NRTI resistance with RPV failures was nearly double that with EFV failures[56].

The most common treatment-emergent NNRTI resistance-associated mutation in the RPV group was E138K, a previously uncommon mutation, followed by K101E, H221Y, V90I, Y181C, and V189I. The prevalence of E138 mutants is very rare in subjects failing NVP- or EFV-based regimens, and E138K was not found in a Spanish database analysis[57]. Most of the resistance-associated mutations selected in RPV failures have a significant impact on etravirine activity, significantly higher than the fold change driven by EFV-selected resistance-associated mutations. Regarding NRTI resistance-associated mutations, M184I was by far the most commonly selected change. The E138K/M184I double mutants are mutually compensatory and have a significant replicative advantage, thereby explaining their frequent occurrence in RPV failures[58]. K65R selection was similar in both arms[54]. The proportion of virologic failures that developed resistance from 48 to 96 weeks was low and similar between groups[52]. Based on this information, RPV has been ranked as an alternative regimen for antiretroviral-naive patients in the US DHHS Guidelines, and its indication restricted to subjects with baseline viral load < 100,000 copies/ml in the EMA label[10].

Reproductive animal studies optimistically show no teratogenic effects (FDA pregnancy category B), but whether RPV can be used safely in pregnant women remains to be seen. Rilpivirine is seemingly associated with fewer side effects and has a better lipid profile than EFV. Therefore, it could also be a good option for virologically suppressed subjects with EFV intolerance. In a pilot study, all 49 subjects switching from EFV/TDF/FTC to RPV/TDF/FTC were virologically suppressed at week 12. The pharmacokinetic analysis indicated that brief EFV inductive effects on RPV metabolism mediated by CYP3A induction may not be clinically relevant in suppressed patients, as subjects had therapeutic levels of EFV or RPV during the switch (Fig. 2). Another study in 20 HIV-negative adults also confirmed that the pharmacokinetic interaction between EFV and RPV during the first weeks of the change do not greatly

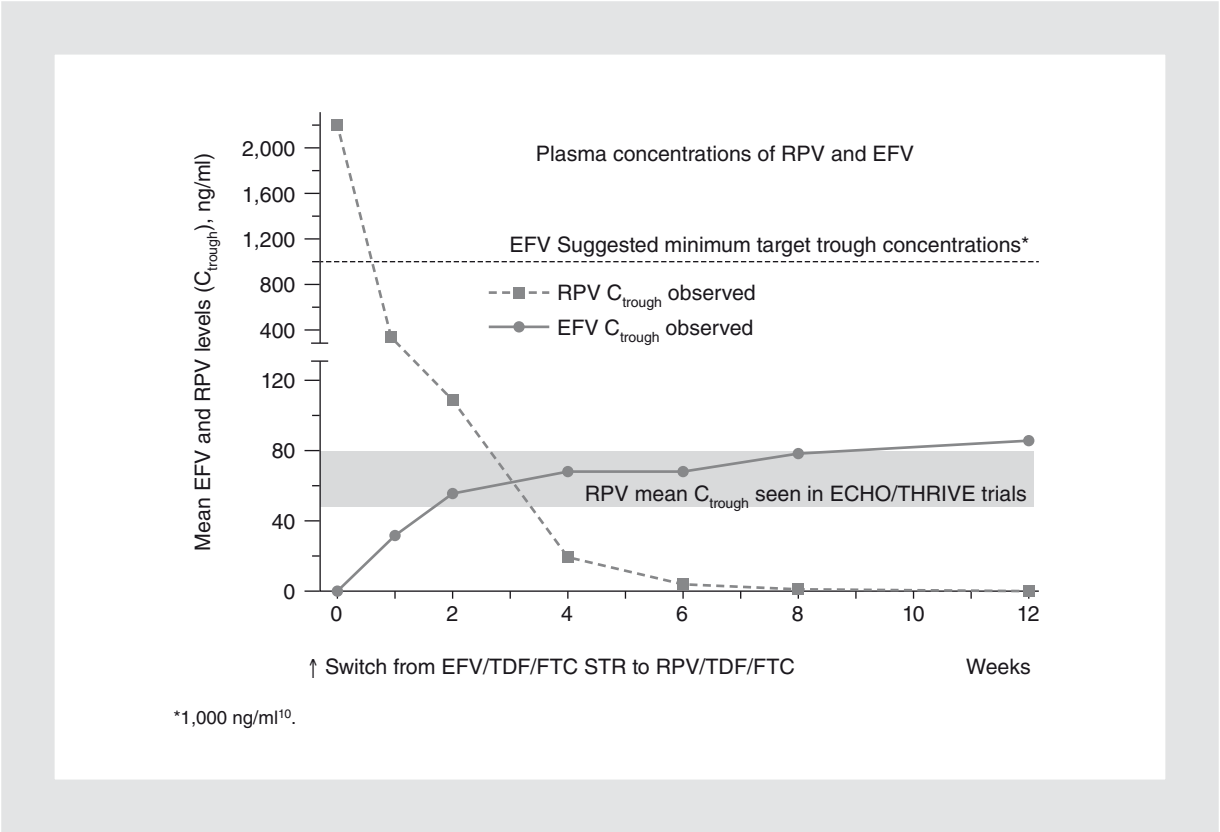

Figure 2. Rilpivirine and efavirenz pharmacokinetics in the setting of switching virologically suppressed HIV-1-infected patients from EFV/TDF/FTC single-tablet regimen to RPV/TDF/FTC single-tablet regimen. Rilpivirine mean C_{trough} remains within target range by two weeks, and EFV mean C_{trough} above IC_{90} (> 10 ng/ml, protein-binding adjusted) for four weeks *(modified from Mills A, et al.[82].)*
RPV: rilpivirine; EFV: efavirenz; TDF: tenofovir disoproxil fumarate; FTC: emtricitabine; STR: single-tablet regimen.

affect the total combined antiviral activity during this period[59]. These data support the safety of a direct switch from EFV to RPV in suitable patients.

Elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine

A STR with COBI (150 mg)-boosted EVG plus TDF/FTC demonstrated bioequivalence to ritonavir-boosted EVG and the individual agents[60]. The discovery of COBI kicks off the pharmacokinetic enhancement of non-PI antiretroviral drugs and a potential alternative to ritonavir boosting. The principal patents for ritonavir expire in two years, at which time companies could produce generic ritonavir that could be co-formulated with other drugs. However, its safety profile, which is well understood after 14 years of experience, may fall short of friendly. In addition, low-dose ritonavir poses a theoretical risk of resistance if ritonavir sees wider use boosting drugs other than PI. Cobicistat is a novel pharmacokinetic enhancer without anti-HIV activity[61]. It selectively inhibits CYP3A (with enzyme kinetic parameters similar to those of ritonavir), the main pathway by which EVG undergoes metabolism in the intestine and liver (secondarily metabolized by glucuronidation). The inhibition of midazolam clearance, a known selective CYP3A probe substrate, was comparable between COBI and ritonavir 100 mg. Cobicistat is also a weak inhibitor of CYP2D6 and has no effect on other major cytochrome isoenzymes or P-glycoprotein. Thus, it seemingly lacks undesirable, off-target drug interactions involving uridine diphospho-glucuronosyltransferase (UGT), P-glycoprotein, and a stronger inhibition and/or induction of CYP2D6[61,62]. On the other hand, extensive clinical experience and pharmacokinetic data with ritonavir boosting and concomitant medications are available. Data regarding the effect of COBI on concomitant medications, particularly CYP3A substrates, are lacking.

Cobicistat inhibits active tubular secretion of creatinine facilitated by the transporter MATE1[63]. Therefore, it is associated with small increases in serum creatinine

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and a corresponding reduction in estimated glomerular filtration rate (GFR) without real changes in actual GFR, confirmed with iohexol-estimated GFR, which exclusively undergoes glomerular filtration and is not secreted or reabsorbed. These changes typically occur within the first days of dosing and resolve upon stopping COBI.

A phase II double-blind, placebo-controlled study demonstrated comparable rates of virologic suppression and CD4 count increases with ATV boosted by either COBI or ritonavir[64]. However, STR containing ATV and COBI are not under development so far.

Elvitegravir (GS-9137) is a potent HIV-1 integrase inhibitor with full activity against NRTI-, NNRTI-, and PI-resistant strains[65]. A phase II dose-ranging study evaluated three doses of ritonavir-boosted EVG in treatment-experienced subjects. Elvitegravir was non-inferior (50 mg) or superior (125 mg) to the comparator PI/r arm in the time-weighted average change in HIV-1 RNA[66]. The EVG 20 mg arm was stopped by the independent data monitoring committee due to higher rates of virologic failure.

In a phase III double-blind study, EVG plus a PI/r in treatment-experienced patients met the criterion for non-inferiority against RAL, with virologic responses through 48 weeks of 59 and 58%, respectively (treatment difference 1·1%; 95% CI: –6.0 to 8.2)[67]. Elvitegravir had a safety profile comparable with RAL, with the advantage of once-daily dosing.

In initial treatment of HIV-1 infection, EVG has been studied in a co-formulated STR containing EVG 150 mg/COBI 150 mg/FTC 200 mg/TDF 300 mg (known as QUAD). The double-blind phase II GS-US-236-0104 study was the first in the history of HIV medicine to compare two STR regimens: QUAD vs. EFV/TDF/FTC in treatment-naive subjects[68]. Participants receiving EVG/COBI/FTC/TDF exhibited a more rapid decline in HIV-1 RNA and a greater proportion suppressed viral load to < 50 copies/ml than participants receiving EFV/TDF/FTC. Administration of QUAD resulted in an unexpectedly high proportion of subjects with suppressed viral load at both 24 and 48 weeks (90 vs. 83% in the EFV/TDF/FTC arm). In addition, once-daily administration of EVG/COBI/FTC/TDF provided a mean EVG C_{trough} 10-fold over its protein binding-adjusted IC_{95} across study visits.

Phase III studies GS-US-236-0102 and GS-US-236-0103 have compared QUAD to both EFV/TDF/FTC and ATV/r plus TDF/FTC in treatment-naive subjects[33,34]. Both randomized studies were conducted in parallel and included 700 subjects each in a double-blind, double-dummy design, randomized 1:1, stratified by HIV-1 RNA (> 100,000 copies/ml), and with an estimated GFR ≥ 70 ml/min (Cockcroft-Gault equation). The primary endpoint was the proportion with HIV-1 RNA < 50 copies/ml at week 48 by US FDA snapshot analysis (12% non-inferiority margin). The mean baseline CD4 cell counts were remarkably high in both studies (391 and 364 in both QUAD arms, respectively, and similar in the comparator arms), and only 12-15% of the subjects in the QUAD arms had ≤ 200 cells/mm^3. QUAD was non-inferior to EFV/TDF/FTC at week 48, with 88 vs. 84% treatment success (difference 3.6; 95% CI: –1.6 to 8.8) (Table 2)[33]. QUAD was also non-inferior to ATV/r plus TDF/FTC at week 48, with 90 vs. 87% treatment success (difference 3.0; 95% CI: –1.9 to 7.8)[34]. These efficacy results are the highest seen so far in phase III studies of ART. Unfortunately, the double-dummy design did not allow investigation of the full advantages of a STR, as all participants took a second placebo STR pill.

In both studies, QUAD efficacy was comparable in high and low HIV-1 RNA and across CD4 cell count baseline strata, even though the cutoff for defining "low" CD4 counts was established at 350 cells/mm^3 due to the low number of subjects with ≤ 200 cells/mm^3. Further studies are needed to clarify the efficacy of QUAD in subjects with ≤ 100 cells/mm^3. Efficacy has been shown across protocol-specified subgroups, including race, gender, and age. The CD4 cell count response was significantly greater with QUAD than with the EFV arm (increase 239 vs. 206 cells/mm^3 at 48 weeks, respectively; $p = 0.009$) and similar to the ATV/r arm.

Toxicity-driven discontinuation rates were low and similar between QUAD and EFV or ATV/r arms. As expected, the QUAD arm experienced significantly less typical EFV-related adverse events (abnormal dreams, insomnia, dizziness, and rash; $p < 0.05$ for all), but nausea was more common with QUAD (21 vs. 14%; $p < 0.05$). Only subjects with HIV-1 RNA ≥ 400 copies/ml were analyzed for HIV-1 resistance, with low rates in both QUAD arms (4 and 3% in the 102 and 103 studies, respectively), as well as in the EFV (5%) and ATV/r (2%) arms. Although this represents a very low number of treated patients, the behavior of these three regimens upon virologic failure, and therefore their genetic barriers to resistance, is dissimilar.

In the pooled analysis, virologic failures in the QUAD arms had selected integrase resistance mutations (mainly E92Q, Q148R, and N155H, and occasionally T66I) in all subjects showing any resistance mutation (13 out of 26 subjects were analyzed), together with M184V/I in all, and K65R in one of every three. In the EFV/TDF/FTC arm, NNRTI mutations developed in all

Table 2. Main efficacy data of pivotal phase III studies evaluating new single-tablet regimens or components in treatment-naive HIV-1-infected individuals (all studies have included co-formulated nucleoside/tide reverse transcriptase inhibitors)

Study Code	Third drug	NRTI	N	Viral load < 50 c/ml at 48 weeks*	AE D/C rates	STR used in study
ECHO[32]	RPV	TDF/FTC	346	83%	2%	No
	EFV	TDF/FTC	344	83%	7%	No
THRIVE[37]	RPV	TDF/FTC, ZDV/3TC,	340	86%	3%	No
	EFV	or ABC/3TC†	338	82%	7%	No
GS-US-236-0102[33]	EVG	TDF/FTC	348	88%‡	3.5%	Yes
	EFV	TDF/FTC	352	84%‡	5.1%	Yes
GS-US-236-0102[34]	EVG	TDF/FTC	353	90%‡	3.7%	Yes
	ATV/r	TDF/FTC	355	87%‡	5.1%	No
SPRING-2[38]	DTG	ABC/3TC	411	88%	2%	No
	RAL	or TDF/FTC	411	85%	2%	No

*ITT-TLOVR unless otherwise specified.
†60, 30, and 10% respectively, in both arms.
‡FDA snapshot analysis. Arms receiving single-tablet regimens shaded in light grey.
NRTI: nucleoside/tide reverse transcriptase inhibitors; N: number of subjects randomized and treated; AE D/C rates: toxicity-driven discontinuation rates at 48 weeks; STR: single-tablet regimen used through the study; RPV: rilpivirine; EVG: elvitegravir; TDF: tenofovir disoproxil fumarate; FTC: emtricitabine; EFV: efavirenz; ATV/r ritonavir-boosted atazanavir; DTG: dolutegravir; RAL: raltegravir; ZDV: zidovudine; 3TC: lamivudine; ABC: abacavir.

subjects showing any resistance mutation (8 out of 17 subjects were analyzed) and NRTI mutations (M184V/I or K65R) developed in half. On the other hand, no subject treated with ATV/r plus TDF/FTC (n = 355) selected any PI or NRTI resistance mutations, in agreement with prior results seen in the CASTLE and ACTG 5202 trials[19,27]. With the pattern of mutations selected in EVG-treated subjects, DTG would be a suitable option in all of them, as long as treatment is withdrawn early on virologic failure and further mutations, such as Q148R, do not accumulate (seen in one subject)[69].

Not unexpectedly, QUAD was associated in both studies with a 48-week median increase in serum creatinine of 0.12-0.14 mg/dl, which was greater compared to EFV (0.01 mg/dl; $p < 0.001$) and ATV/r (0.08 mg/dl; $p < 0.001$), albeit it lacked clinical significance. The increase was apparent at week 2 and remained stable thereafter. Five (1.4%) and one subjects discontinued QUAD in studies 102 and 103, respectively, due to renal events, compared to none in the EFV arm and one in the ATV/r arm.

QUAD displayed a safe lipid profile, with significantly lower increases in total, HDL, and LDL cholesterol than EFV ($p \leq 0.001$ for all them, although the total/HDL cholesterol ratio remained unchanged), and a lower triglyceride increase than ATV/r ($p < 0.006$). Finally, bone mineral density changes at both spine and hip were similar between QUAD and the ATV/r arm[34]. The non-inferiority demonstrated in these studies suggests that QUAD may be another suitable option for STR in patients with high or low viral load.

Concentrations of EVG remained in a range consistent with potent anti-HIV activity in 32 healthy volunteers after a switch from EFV/TDF/FTC (EFV induces both CYP3A and UGT)[70]. Elvitegravir C_{trough} levels were about threefold above 45 ng/ml (the protein binding-adjusted wild-type HIV-1 IC_{95}) immediately after the switch (one week) and the EVG AUC was lower (63.1%), showing a continuous increase thereafter. A phase IIIb trial assessing a switch from an NNRTI plus TDF/FTC (including EFV and RPV) to QUAD is underway[71].

A new combination including EVG/FTC/COBI/GS-7340 is also under study. GS-7340 is a novel prodrug of tenofovir, which leads to significantly greater decreases in HIV-1 RNA compared with TDF 300 mg, with 86% lower plasma tenofovir exposures (AUC), and sevenfold higher intracellular tenofovir-diphosphate concentrations both in PBMC and lymphatic tissues, compared with TDF 300 mg in 10-day monotherapy studies[72-74]. This could allow a significant reduction in the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity. Furthermore, COBI doubles to triple exposure of GS-7340 when co-formulated with EVG/FTC/COBI/GS-7340, driving tenofovir exposures much higher than with GS-7340 alone[75]. The AUC of GS-7340 shows a 222 (95% CI: 200-246) increase, and C_{max} a 223 (187-265) increase, probably through COBI inhibition of intestinal

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P-glycoprotein-mediated secretion of GS-7340. In the same study, GS-7340 at 10 mg in the 4-in-1 tablet yielded similar GS-7340 exposure as GS-7340 at 25 mg with FTC. These findings suggest that a co-formulation including COBI and GS-7340 could contain as little as 10 mg of GS-7340 (instead of 300 mg of TDF).

Dolutegravir/lamivudine/abacavir

Dolutegravir (S/GSK1349572) is the first integrase inhibitor dosed once daily without pharmacokinetic boosting. It has a higher barrier to resistance compared to RAL and EVG, retaining activity against many viral strains harboring major integrase resistance mutations selected for by both of them. In a phase IIa study, mean decreases in HIV-1 RNA of 1.51-2.46 $\log_{10}$ copies/ml were observed with 10-day DTG monotherapy[76]. A well characterized dose-response relationship was observed for viral load decrease, and antiviral response was sustained between day 11 and 14, despite discontinuation on day 10. Amazingly, most patients (7 of 10; 70%) receiving DTG 50 mg achieved plasma HIV-1 RNA < 50 copies/ml.

In a phase IIb dose-ranging study in treatment-naive adults, doses of 10, 25, or 50 mg once daily were effective and well tolerated at all assessed doses, with either TDF/FTC or ABC/3TC; EFV was the comparator drug[77]. Three virologic failures were identified among 155 subjects treated with DTG, and no integrase mutations were selected in any of them. The proportion of participants with viral load < 50 copies/ml at 48 weeks (ITT-TLOVR algorithm) in subjects treated with DTG was an impressive 88-91% (82% in the EFV arm)[69]. As seen with other integrase inhibitors, initial viral load decay and achievement of viral suppression occurred significantly faster in the DTG arm through week 24[28,33,34].

More participants in the EFV group experienced well described neuropsychiatric adverse events and rash and discontinued because of tolerability or safety events. Small, non-progressive increases in serum creatinine were recorded across DTG doses, consistent with the strong pharmacological inhibition of tubular creatinine secretion via the organic cation transporter OCT2 (similar to cimetidine or trimethoprim), with no significant effect on actual GFR[69].

The 50 mg once-daily dose was chosen for phase III trials with treatment-naive subjects, while 50 mg twice daily was selected for pretreated subjects[78]. A phase III study (SPRING-2) has included 822 HIV-1-infected treatment-naive participants. The study compares the efficacy and safety of DTG and RAL, both administered with either ABC/3TC or TDF/FTC. Although confirmation of the results is necessary, a company press release has announced that DTG demonstrates non-inferiority to RAL[38]. Through 48 weeks, 88% of study participants on DTG were virologically suppressed (< 50 copies/ml) vs. 85% of participants on RAL (95% CI for the difference: –2.2% to 7.1%). The tolerability of DTG was similar to that of RAL, with rates of adverse events leading to withdrawal of 2% in both arms. Obviously, the efficacy results seen in subjects treated with ABC/3TC will be analyzed with special interest, particularly those with high baseline viral load. If no caveats are encountered, a STR containing DTG/ABC/3TC has the potential to constitute the first STR without TDF/FTC and a suitable option in HLA-B*5701-negative subjects without hepatitis B coinfection.

Darunavir/cobicistat/emtricitabine/GS-7340

Gilead Sciences has entered into a license agreement with Tibotec Pharmaceuticals for the development and commercialization of a STR combining DRV with COBI, the investigational agent GS-7340, and FTC. If approved, it will be the first time a STR would include a PI that with 800 mg poses fabulous challenges to Galenic developers. Pharmacokinetic studies indicate that least square mean ratios were virtually identical for DRV (800 mg once-daily) C_{max} and AUC_{24h} boosted by either 100 mg of ritonavir or 150 mg of COBI (90% CI for those comparisons were all within 80 to 125%, which indicates bioequivalence)[79,80]. Darunavir C_{trough} concentrations were 26% lower with COBI 150 mg than with ritonavir (least square means ratio 0.74; 90% CI: 0.63-0.86). On the basis of limited data on DRV troughs below 550 ng/ml and modeling studies that suggest no loss of antiviral activity with a 50% drop in C_{trough}, the researchers do not consider these moderately lower DRV troughs with COBI to be clinically relevant. However, they do fall outside the generally accepted bioequivalence range of 80 to 125%.

The small mass of GS-7340 (one tenth of TDF 300 mg) has been of great help in the compaction of the ingredients. This novel prodrug of tenofovir led to significantly greater decreases in HIV-1 RNA, compared with TDF 300 mg, with 86% lower plasma tenofovir exposures (AUC), and sevenfold higher intracellular tenofovir-DP concentrations both in PBMC and lymphatic tissues, compared with TDF 300 mg in 10-day monotherapy studies[72-74]. This could reduce the total dose of tenofovir, thereby minimizing systemic exposure, while at the same time increasing antiviral activity. It remains to

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be seen if the double to triple exposures of GS-7340 driven by COBI when co-formulated with EVG and FTC are also observed when co-formulated with DRV and FTC[75]. Cobicistat could inhibit the intestinal P-glycoprotein-mediated secretion of GS-7340, and a co-formulation including COBI and as little as 10 mg of GS-7340 could provide tenofovir exposures similar to GS-7340 alone at 25 mg.

A phase II study (GS-US-299-0102) is recruiting 150 subjects to compare the efficacy of DRV/COBI/FTC/GS-7340 against DRV/COBI/FTC/TDF[81]. The phase II study GS-US-292-0102 will compare the efficacy and safety of QUAD vs. EVG/COBI/FTC/GS-7340.

Conclusions

Once-daily STR embody the highest level of ART simplification achieved so far. Galenic research and industry patent agreements allow for the availability of STR based on NNRTI (EFV or RPV), integrase inhibitors (COBI-boosted EVG, DTG), and protease inhibitors (COBI-boosted DRV), combined with either FTC/TDF or ABC/3TC. Many HIV-1-infected treatment-naive and pretreated subjects may soon have many options to control their virus with safe one pill once-daily regimens.

Potential conflicts of interest

Josep M. Llibre has received funding for research or payment for conferences or participation on advisory boards from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Jansen-Cilag, Merck Sharp & Dohme, Tibotec, and ViiV Healthcare.

Bonaventura Clotet has served during the past two years as a consultant on advisory boards or participated in speakers' bureaus or conducted clinical trials with BMS, Abbott, Gilead, Janssen, Merck, Siemens and ViiV.

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