

# Dolutegravir: A New Integrase Strand Transfer Inhibitor for the Treatment of HIV

Bhavik M. Shah,<sup>1\*</sup> Jason J. Schafer,<sup>1</sup> and Joseph A. DeSimone, Jr.<sup>2</sup>

<sup>1</sup>Department of Pharmacy Practice, Jefferson School of Pharmacy, Thomas Jefferson University, Philadelphia, Pennsylvania; <sup>2</sup>Division of Infectious Diseases, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

The first two integrase strand transfer inhibitors (INSTIs) approved for treatment of patients infected with human immunodeficiency virus (HIV) were raltegravir and elvitegravir. Both raltegravir and elvitegravir are now guideline-preferred agents as part of an antiretroviral regimen for treatment-naïve patients. However, raltegravir is dosed twice/day. Elvitegravir is available in a single-tablet regimen and dosed once/day because it is administered with the pharmacokinetic booster cobicistat, a potent CYP3A4 inhibitor that can lead to clinically significant drug–drug interactions. In addition, raltegravir and elvitegravir have a low genetic barrier to resistance and are associated with cross-resistance. Dolutegravir is a new-generation INSTI administered once/day without a pharmacokinetic booster and can be coformulated in a single-tablet regimen. Phase III studies have demonstrated the efficacy and safety of dolutegravir for treatment-naïve and treatment-experienced patients. Compared with other INSTIs, dolutegravir has a higher genetic barrier to resistance. Dolutegravir was approved by the U.S. Food and Drug Administration in August 2013 and joins raltegravir and elvitegravir as guideline-preferred agents for the management for HIV-infected treatment-naïve patients.

**KEY WORDS** dolutegravir, DTG, S/GSK1349572, integrase inhibitor, integrase strand transfer inhibitor, INSTI, elvitegravir, raltegravir.

(Pharmacotherapy 2014;34(5):506–520) doi: 10.1002/phar.1386

Raltegravir is the first member of the novel integrase strand transfer inhibitor (INSTI) class. After its approval in 2007, raltegravir became the first INSTI to be listed as a preferred agent in the Department of Health and Human Services (DHHS) guidelines for the management of human immunodeficiency virus (HIV) infection in treatment-naïve patients and is an option for treatment-experienced patients.<sup>1</sup> Raltegravir is administered twice/day, which is not ideal.<sup>2, 3</sup> Patients with HIV infection prefer once/day regimens, especially single-tablet regimens.<sup>4–6</sup> A second INSTI, elvitegravir, was approved in 2012 and is available as a single-tablet regimen containing cobicistat, tenofovir, and emtricitabine.<sup>7</sup> This

single-tablet regimen containing elvitegravir has recently become a preferred regimen for treatment-naïve patients by the DHHS.<sup>8</sup> One of the disadvantages of elvitegravir is its short half-life, which necessitates the administration of the pharmacokinetic booster cobicistat for elvitegravir to be dosed once/day.<sup>9</sup> Cobicistat is a specific and potent inhibitor of CYP3A4 and associated with clinically significant drug–drug interactions.<sup>9</sup> The second-generation INSTI dolutegravir (S/GSK 1349572) combines the advantages of its predecessors, but it is administered once/day without the need for a pharmacokinetic booster and may be coformulated with other antiretrovirals in a single-tablet regimen.<sup>10, 11</sup> Dolutegravir has been investigated as part of an antiretroviral therapy (ART) regimen for treatment-naïve and treatment-experienced patients.<sup>12–18</sup> This article reviews the pharmacology, clinical safety and efficacy, and potential place in therapy of dolutegravir.

\*Address for correspondence: Bhavik M. Shah, Jefferson School of Pharmacy, 901 Walnut Street, Suite 901, Philadelphia, PA 19107; e-mail: bhavik.shah@jefferson.edu.  
© 2013 Pharmacotherapy Publications, Inc.

## Pharmacology

The integrase enzyme is one of three virally encoded enzymes essential for HIV replication and is responsible for integrating HIV DNA into the host cell genome.<sup>19</sup> The integration process begins with HIV entry into CD4<sup>+</sup> cells and transcription of viral RNA into complementary viral DNA. First the integrase enzyme binds to a new viral DNA transcript to form the preintegration complex. The enzyme then removes a nucleotide from each viral DNA terminus to expose reactive 3' hydroxyl groups. The complex then enters the host cell nucleus where DNA strand transfer occurs. In this step, the integrase enzyme binds to the host cell DNA and cuts each DNA strand to expose 5' phosphate groups that can become covalently bound to the 3' viral DNA hydroxyl groups formed by the preintegration complex. Once the strand transfer process is complete, host cell enzymes repair any remaining gaps between the viral and host cell DNA.

The INSTIs, including dolutegravir, specifically block the strand transfer step of the integration process.<sup>19</sup> The active site of the integrase enzyme binds to the host cell DNA and includes two divalent metal cations that serve as chelation targets for the INSTIs.<sup>10, 19</sup> As a result, when an INSTI is present, the active site of the enzyme is occupied and the integration process is halted.

## Pharmacokinetics and Drug Interactions

The pharmacokinetic (PK) properties of dolutegravir have been studied in healthy volunteers and HIV-infected persons.<sup>10, 20</sup> Two randomized, double-blind, placebo-controlled, single- or multiple-dose escalation studies of dolutegravir oral suspension were conducted in 52 healthy volunteers.<sup>10</sup> The single-dose study consisted of two different cohorts, each with 10 volunteers (active drug, *n* = 8; placebo, *n* = 2). The first cohort received 2, 10, and 50 mg; the second cohort received 5, 25, and 100 mg. In the multiple-dose study, three cohorts received dolutegravir once/day for 10 days in doses of 10 mg (active drug, *n* = 8; placebo, *n* = 2), 25 mg (active drug, *n* = 10; placebo, *n* = 2), or 50 mg (active drug, *n* = 8; placebo, *n* = 2).<sup>10</sup> Dolutegravir was rapidly absorbed with a median time to maximum concentration (*T*<sub>max</sub>) of 1 hour, which is similar to both raltegravir (1 hour) and elvitegravir (2–3 hours) (Table 1).<sup>21, 22</sup> Steady state was reached by day 5, and

Table 1. Pharmacologic properties of HIV-1 integrase strand transfer inhibitors<sup>10, 20–22</sup>

| Drug         | Formulation                                                                                                                          | Dosing                                              | Primary metabolism | <i>T</i> <sub>max</sub> , hrs | Half-life, hrs | Protein binding | Inhibitory concentration, µg/ml | PK parameter associated with efficacy |
|--------------|--------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|--------------------|-------------------------------|----------------|-----------------|---------------------------------|---------------------------------------|
| Raltegravir  | 400-mg tablet;<br>100-mg chewable tablet;                                                                                            | Adult: 400 mg twice/day<br>Child: 6 mg/kg twice/day | UGT 1A1            | 1                             | 7–12           | 83%             | IC <sub>95</sub> = 0.016        | Unknown                               |
| Elvitegravir | 25-mg chewable tablet<br>Combination tablet:<br>Elvitegravir 150 mg<br>Tenofovir 300 mg<br>Emtricitabine 200 mg<br>Cobicistat 150 mg | 1 tablet/day                                        | CYP 3A4            | 2–3                           | 9              | 99%             | IC <sub>95</sub> = 0.045        | <i>C</i> <sub>min</sub>               |
| Dolutegravir | 50-mg tablet;<br>Combination tablet:<br>Dolutegravir 50 mg<br>Abacavir 600 mg<br>Lamivudine 300 mg                                   | 1 tablet/day                                        | UGT 1A1            | 1–2                           | 13–15          | 99.3%           | IC <sub>90</sub> = 0.064        | <i>C</i> <sub>min</sub>               |

PK = pharmacokinetic; UGT = uridine diphosphate-glucuronosyltransferase; CYP = cytochrome P450 enzyme; IC = inhibitory concentration; *C*<sub>min</sub> = concentration at the end of a dosing interval.

drug accumulation was modest. Importantly, the geometric mean steady state concentration at the end of the 50-mg dosing interval ( $C_{\min}$ ) was 1.6  $\mu\text{g/ml}$  or 25-fold higher than the protein-adjusted 90% inhibitory concentration (0.064  $\mu\text{g/ml}$ ). Combined with an observed 13–15 hour half-life (raltegravir, 7–12 hours; elvitegravir, 9 hours), these  $C_{\min}$  levels suggest that once/day dosing is appropriate. Additionally, only low to moderate intersubject variability was observed for the multiple PK parameters assessed in these studies. This observation suggests PK similarities between dolutegravir and elvitegravir but differences with raltegravir, for which significant variability has been observed.<sup>23, 24</sup> The investigators postulate that the more predictable PK profile observed with dolutegravir in comparison with raltegravir could prevent extremes of drug exposures that might result in toxicity or therapeutic failure.<sup>10</sup> Their conclusion should be interpreted with caution, however, because there is no evidence to suggest that the plasma-level variability with raltegravir results in poor patient outcomes.

The PK properties of dolutegravir have also been characterized in HIV-infected persons.<sup>20</sup> A phase I randomized, double-blind, placebo-controlled study of dolutegravir monotherapy enrolled 35 treatment-naïve or treatment-experienced men. After a 10-hour fast, dolutegravir was administered once/day for 10 consecutive days. Patients were divided into four groups that received 2 mg ( $n = 9$ ), 10 mg ( $n = 9$ ), 50 mg ( $n = 10$ ), or placebo ( $n = 7$ ). Dolutegravir was rapidly absorbed (mean  $T_{\max} = 1.5$ –2.5 hours) with a mean half-life of 12 hours and a time to steady state concentration of 7 days.

There was minimal intersubject variability in dolutegravir PK.<sup>20</sup> At steady state, the 50-mg dose achieved a mean  $C_{\max}$  of 3.34  $\mu\text{g/ml}$  (16% coefficient of variation), an area under the curve ( $\text{AUC}_{0-24 \text{ h}}$ ) of 43.4  $\mu\text{g}\cdot\text{h/ml}$  (coefficient of variation 20%), and a  $C_{\min}$  of 0.83  $\mu\text{g/ml}$  (coefficient of variation 26%). The  $C_{\min}$  was higher than the adjusted 90% inhibitory concentration and was the parameter that best predicted viral load response.<sup>20</sup> This observation again draws parallels with elvitegravir, but it distinguishes dolutegravir from raltegravir because plasma exposure of raltegravir does not correlate with clinical outcomes.<sup>24, 25</sup> By day 11, significant reductions in plasma HIV-RNA were observed for all dolutegravir dose groups compared with placebo (mean decrease 1.51–2.46  $\log_{10}$  copies/ml,  $p < 0.001$ ). Reductions were particularly profound for the 50-mg group in which 70% of

patients achieved plasma HIV RNA below 50 copies/ml. These patients also maintained viral suppression for 4 days after discontinuing dolutegravir,<sup>20</sup> likely because plasma levels remained above the 50% inhibitory concentration (0.016  $\mu\text{g/ml}$ ) during this time period. This level of virologic response was similar to findings of short-term studies of other antiretrovirals and supported evaluation of the long-term efficacy of dolutegravir in combination with other antiretroviral agents in larger clinical trials.<sup>23, 24</sup>

The currently recommended dose of dolutegravir is 50 mg once/day for INSTI-naïve patients.<sup>26</sup> More than half of an administered dose (53%) is eliminated unchanged in the feces; nearly a third (31%) is eliminated as metabolites in the urine.<sup>27</sup> Metabolism primarily occurs (51%) through uridine diphosphate-glucuronosyltransferase (UGT) 1A1 with minor contributions from cytochrome (CYP) 3A4 (21%), UGT 1A9 (6%), and UGT 1A3 (3%).<sup>10, 27</sup> Dolutegravir is also a substrate for p-glycoprotein. In vitro, dolutegravir does not induce or inhibit commonly used metabolic pathways and is therefore not expected to cause interactions with drugs that are P-glycoprotein, UGT, or CYP P450 enzyme substrates.<sup>27</sup> However, potent inducers and/or inhibitors of UGT 1A1 and CYP3A4 can significantly alter dolutegravir concentrations. For example, rifampin induces both UGT-1A1 and CYP3A4, and coadministration significantly reduces dolutegravir levels.<sup>28</sup> A phase I drug interaction study in healthy volunteers demonstrated that it was necessary to increase the dolutegravir dosage to 50 mg twice/day when coadministered with rifampin 600 mg/day to achieve dolutegravir concentrations similar to those attained during once/day dosing. Dolutegravir concentrations did not change during administration of rifabutin 300 mg once/day, suggesting that dosing adjustments are not necessary when these agents are coadministered.<sup>28</sup>

Many antiretroviral agents can also induce or inhibit CYP3A4 or UGT 1A1 enzymes and could alter dolutegravir concentrations during coadministration (Table 2). For example, the combination of dolutegravir with the UGT 1A1 inhibitor atazanavir/ritonavir or atazanavir alone in a small study of healthy volunteers showed that dolutegravir AUC levels increased by 69% and 91%,  $C_{\max}$  levels increased by 34% and 50%, and  $C_{\min}$  levels increased by 121% and 180%, respectively.<sup>29</sup> These changes were not considered clinically significant and did not translate to additional adverse events. The investigators

Table 2. Dolutegravir drug interactions<sup>28–37, 40</sup>

| Drug                                       | Study details                                                                                                                                                                                                                                            | Effect on dolutegravir or concomitant drug concentrations                                                                                                                                                                                                                                                                                                                          | Dosing recommendations <sup>a</sup>                                                                                                |
|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| <b>PI</b>                                  |                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                    |
| Atazanavir<br>400 mg/day                   | Open label, crossover design<br>Dolutegravir 30 mg/<br>day × 14 days<br>Healthy subjects (n = 12)                                                                                                                                                        | Dolutegravir AUC, C <sub>max</sub><br>and C <sub>min</sub> increased 91%,<br>50%, and 180%                                                                                                                                                                                                                                                                                         | No dosing adjustments<br>necessary                                                                                                 |
| Atazanavir/r<br>300 mg/100 mg/day          | Open-label crossover design<br>Dolutegravir 30 mg/<br>day × 14 days<br>Healthy subjects (n = 12)                                                                                                                                                         | Dolutegravir AUC, C <sub>max</sub><br>and C <sub>min</sub> increased 62%,<br>34%, and 121%                                                                                                                                                                                                                                                                                         | No dosing adjustments<br>necessary                                                                                                 |
| Darunavir/r<br>600 mg/100 mg twice/day     | Open-label crossover design<br>Dolutegravir 30 mg/<br>day × 14 days<br>Healthy subjects (n = 15)                                                                                                                                                         | Dolutegravir AUC, C <sub>max</sub><br>and C <sub>min</sub> decreased 22%,<br>11%, and 38%                                                                                                                                                                                                                                                                                          | No dosing adjustments<br>necessary                                                                                                 |
| Fosamprenavir/r<br>700 mg/100 mg twice/day | Open-label crossover design<br>Dolutegravir 50 mg/<br>day × 15 days<br>Healthy subjects (n = 12)                                                                                                                                                         | Dolutegravir AUC, C <sub>max</sub><br>and C <sub>min</sub> decreased 35%,<br>24%, and 49%                                                                                                                                                                                                                                                                                          | Dolutegravir 50 mg<br>twice/day for INSTI-<br>naive patients <sup>b</sup>                                                          |
| Lopinavir/r<br>400 mg/100 mg twice/day     | Open-label crossover design<br>Dolutegravir 30 mg/<br>day × 14 days<br>Healthy subjects (n = 15)                                                                                                                                                         | No significant effects                                                                                                                                                                                                                                                                                                                                                             | No dosing adjustment<br>necessary                                                                                                  |
| Tipranavir/r<br>500 mg/200 mg twice/day    | Open-label crossover design<br>Dolutegravir 50 mg/<br>day × 5 days<br>Healthy subjects (n = 18)                                                                                                                                                          | Dolutegravir AUC, C <sub>max</sub><br>and C <sub>min</sub> decreased 59%,<br>46%, and 76%                                                                                                                                                                                                                                                                                          | Dolutegravir 50 mg<br>twice/day for INSTI-<br>naive patients <sup>b</sup>                                                          |
| <b>NNRTI</b>                               |                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                    |
| Efavirenz<br>600 mg/day                    | Open-label crossover design<br>Dolutegravir 50 mg/<br>day × 14 days<br>Healthy subjects (n = 12)                                                                                                                                                         | Dolutegravir AUC, C <sub>max</sub><br>and C <sub>min</sub> decreased 57%,<br>39%, and 75%                                                                                                                                                                                                                                                                                          | Dolutegravir 50 mg<br>twice/day for INSTI-<br>naive patients <sup>b</sup>                                                          |
| Etravirine<br>200 mg twice/day             | Open-label crossover design<br>Dolutegravir 50 mg/<br>day × 14 days alone (n = 16)<br>or in combination with either:<br>darunavir/r 600 mg/100 mg<br>twice/day (n = 9) or<br>lopinavir/r 400 mg/100 mg<br>twice/day (n = 8)<br>Healthy subjects (n = 33) | Dolutegravir AUC, C <sub>max</sub><br>and C <sub>min</sub> decreased 71%,<br>52%, and 88%<br>Dolutegravir AUC, C <sub>max</sub><br>and C <sub>min</sub> decreased 25%,<br>12%, and 37% with<br>etravirine plus darunavir/<br>ritonavir<br>Dolutegravir AUC, C <sub>max</sub><br>and C <sub>min</sub> increased 11%,<br>7%, and 28% with<br>etravirine plus lopinavir/<br>ritonavir | Do not coadminister<br>dolutegravir and<br>etravirine unless either<br>darunavir or lopinavir<br>is included in the ART<br>regimen |
| Rilpivirine<br>25 mg/day                   | Open-label crossover design<br>Dolutegravir 50 mg/<br>day × 5 days                                                                                                                                                                                       | No significant effects                                                                                                                                                                                                                                                                                                                                                             | No dosing adjustments<br>necessary                                                                                                 |
| <b>NRTI</b>                                |                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                    |
| Tenofovir<br>300 mg/day                    | Open-label crossover design<br>Dolutegravir 50 mg/<br>day × 5 days<br>Healthy subjects (n = 15)                                                                                                                                                          | No significant effects                                                                                                                                                                                                                                                                                                                                                             | No dosing adjustments<br>necessary                                                                                                 |
| <b>Hepatitis C PI</b>                      |                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                    |
| Boceprevir<br>800 mg 3 times/day           | Open-label crossover design<br>Dolutegravir 50 mg/<br>day × 10 days<br>Healthy subjects (n = 16)                                                                                                                                                         | No significant effects                                                                                                                                                                                                                                                                                                                                                             | No dosing adjustments<br>necessary                                                                                                 |
| Telaprevir<br>750 mg 3 times/day           | Open-label crossover design<br>Dolutegravir 50 mg/<br>day × 10 days<br>Healthy subjects (n = 16)                                                                                                                                                         | Dolutegravir AUC, C <sub>max</sub><br>and C <sub>min</sub> increased 25%,<br>19%, and 37%                                                                                                                                                                                                                                                                                          | No dosing adjustments<br>necessary                                                                                                 |

(continued)

Table 2. (continued)

| Drug                                                   | Study details                                                                                                                                                                                                                                                            | Effect on dolutegravir or concomitant drug concentrations                                                                                                                                   | Dosing recommendations <sup>a</sup>                               |
|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| <b>Rifamycins</b>                                      |                                                                                                                                                                                                                                                                          |                                                                                                                                                                                             |                                                                   |
| Rifabutin<br>300 mg/day                                | Open-label crossover design<br>Dolutegravir 50 mg/<br>day × 14 days<br>Healthy subjects (n = 9)                                                                                                                                                                          | No change in dolutegravir<br>AUC or C <sub>max</sub> ; C <sub>min</sub><br>decreased by 30%                                                                                                 | No dosing adjustments<br>necessary                                |
| Rifampin<br>600 mg/day                                 | Open-label crossover design<br>Dolutegravir 50 mg/<br>day × 7 days<br>Followed by twice/<br>day × 14 days with rifampin<br>Healthy subjects (n = 12)                                                                                                                     | Dolutegravir AUC, C <sub>max</sub><br>and C <sub>min</sub> increased 33%,<br>18%, and 22% with<br>dolutegravir 50 mg twice/<br>day plus rifampin<br>compared with<br>dolutegravir 50 mg/day | Dolutegravir<br>50 mg twice/day <sup>2</sup>                      |
| <b>Acid-reducing agents</b>                            |                                                                                                                                                                                                                                                                          |                                                                                                                                                                                             |                                                                   |
| Antacids<br>20 ml × 1 dose                             | Open-label crossover design<br>Dolutegravir 50 mg × 1<br>either simultaneously with<br>antacid or 2 hrs prior to<br>antacid<br>Healthy subjects (n = 16)                                                                                                                 | Dolutegravir AUC, C <sub>max</sub><br>and C <sub>min</sub> decreased 74%,<br>72%, and 74% with<br>simultaneous dose versus<br>dose 2 hrs prior to antacid                                   | Administer antacids<br>6 hrs prior or<br>2 hrs after dolutegravir |
| Omeprazole<br>40 mg/day × 5 days                       | Open-label crossover design<br>Dolutegravir 50 mg × 1 on<br>day 5 of omeprazole<br>Healthy subjects (n = 12)                                                                                                                                                             | No significant effects                                                                                                                                                                      | No dosing<br>adjustments necessary                                |
| <b>Oral contraceptive agents</b>                       |                                                                                                                                                                                                                                                                          |                                                                                                                                                                                             |                                                                   |
| Ethinyl estradiol 0.035 mg<br>and norgestimate 0.25 mg | Randomized, double-blind,<br>placebo-controlled, crossover<br>design<br>Dolutegravir 50 mg twice/day<br>or placebo on days 1–10 or<br>12–21 within a single<br>menstrual cycle and while<br>receiving oral contraceptive<br>agent<br>Healthy female subjects<br>(n = 12) | No significant effects                                                                                                                                                                      | No dosing<br>adjustments necessary                                |
| <b>Opioid addiction agent</b>                          |                                                                                                                                                                                                                                                                          |                                                                                                                                                                                             |                                                                   |
| Methadone                                              | Open-label crossover design<br>Dolutegravir 50 mg twice/<br>day × 5 days<br>Opiate-dependent HIV-<br>negative subjects (n = 12)                                                                                                                                          | No significant effects                                                                                                                                                                      | No dosing adjustments<br>necessary                                |

PI = protease inhibitor; AUC = area under the curve; C<sub>max</sub> = maximum concentration; C<sub>min</sub> = concentration at the end of a dosing interval; /r = ritonavir; INSTI = integrase strand transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; ART = antiretroviral therapy; NRTI = nucleoside reverse transcriptase inhibitor; HIV = human immunodeficiency virus.

<sup>a</sup>Standard dolutegravir dosing is 50 mg once/day.

<sup>b</sup>Consider an alternative combination for INSTI-experienced patients with confirmed or suspected INSTI resistance.

concluded that these agents could be coadministered safely without dosing adjustments.<sup>29</sup>

Potential drug interactions between dolutegravir and other ritonavir-boosted HIV protease inhibitors (PIs) including lopinavir, fosamprenavir, darunavir, and tipranavir have been studied.<sup>30–32</sup> Unlike atazanavir, these agents are not UGT 1A1 inhibitors, but they are always administered in combination with ritonavir, which is a potent CYP3A4 and p-glycoprotein inhibitor and a UGT 1A1 inducer. In studies of healthy

volunteers, coadministration of dolutegravir and either darunavir/ritonavir or lopinavir/ritonavir resulted in modest and clinically insignificant reductions in steady state dolutegravir concentrations. In each case, dolutegravir C<sub>min</sub> levels exceeded the protein binding adjusted 90% inhibitory concentration and were consistent with concentrations associated with virologic efficacy in a previously described phase I study.<sup>10, 30</sup> Significant reductions in dolutegravir concentrations occur during concurrent fosamprenavir/ritonavir

or tipranavir/ritonavir administration, but according to the manufacturer this drug interaction can be mitigated by adjusting dolutegravir to twice/day dosing.<sup>26</sup> These data suggest that combinations of dolutegravir and commonly used HIV PIs can be safely administered to patients, although dolutegravir may need to be administered twice/day instead of once/day. Treatment-naïve patients are not appropriate candidates for combination therapy. Rather, combination therapy is more likely for treatment-experienced patients whose options are limited because of resistance to ART.

Similarly, the ability to safely combine dolutegravir and nonnucleoside reverse transcriptase inhibitors (NNRTIs) may also be a consideration for treatment-experienced patients. Efavirenz moderately reduced dolutegravir concentrations in healthy volunteers, likely as a result of CYP3A4 and UGT 1A1 induction.<sup>32</sup> These reductions were considered to be clinically relevant by the manufacturer, and a dosing adjustment to dolutegravir 50 mg twice/day is recommended. As with tenofovir, rilpivirine neither induces nor inhibits UGT 1A1 or CYP enzymes, and coadministration with dolutegravir did not result in clinically meaningful changes in concentrations of these antiretrovirals.<sup>33, 34</sup> In contrast, etravirine is an inducer of CYP3A4 and possibly UGT 1A1 and has been found to reduce dolutegravir steady state concentrations significantly.<sup>35</sup> Dolutegravir  $C_{min}$  concentrations declined with etravirine by 88% to a geometric mean of 0.16 µg/ml (84% coefficient of variance), with some dolutegravir concentrations falling below the protein adjusted 90% inhibitory concentration. When the investigators combined dolutegravir and etravirine with either lopinavir/ritonavir or darunavir/ritonavir, dolutegravir concentrations were similar to those observed when it was administered with either PI alone. As a result, the investigators concluded that etravirine and dolutegravir should only be coadministered if either lopinavir/ritonavir or darunavir/ritonavir is also included in the ART regimen.<sup>35</sup>

Drug–drug interactions between other medications and dolutegravir have been investigated. Specifically, dolutegravir does not alter methadone concentrations.<sup>36</sup> Dolutegravir does not significantly interact with oral contraceptives containing norgestimate and ethinyl estradiol.<sup>36</sup> Therefore, in contrast to many other antiretroviral agents, contraceptive efficacy should be maintained during dolutegravir coadministration.

Dolutegravir does not appear to have clinically relevant drug interactions with the hepatitis C PIs telaprevir and boceprevir, both of which are strong CYP3A4 inhibitors that can affect the metabolism of other antiretrovirals and complicate the treatment of HIV and hepatitis C coinfection.<sup>37</sup> Both dolutegravir and raltegravir concentrations are largely unaffected by telaprevir and boceprevir, and each can be coadministered with these hepatitis C PIs without the need for dosing adjustments.<sup>37, 38</sup> In contrast, concomitant administration of boceprevir or telaprevir with ART regimens containing elvitegravir are not recommended because elvitegravir is metabolized via CYP3A4, and clinically significant drug interactions are likely.<sup>1</sup>

Dolutegravir can be administered with or without food, although modest increases in  $T_{max}$  and AUC levels following meals can occur.<sup>39</sup> Because dolutegravir absorption is not pH dependent, dosing adjustments are not needed with coadministration of acid-reducing agents (e.g., omeprazole).<sup>40</sup> Importantly, dolutegravir is subject to chelation interactions with antacids resulting in significant reductions in AUC. It is therefore recommended that dolutegravir be administered 2 hours before or 6 hours after the administration of antacids.<sup>40</sup>

Dolutegravir is highly protein bound (99%) and undergoes extensive hepatic metabolism.<sup>10, 41</sup> The PK profile of dolutegravir has not been evaluated in patients with severe liver disease, but it does not appear to be significantly altered by moderate hepatic impairment (Childs-Pugh class B), and dosage adjustments are not required in this setting.<sup>41</sup> Renal clearance of active drug is a minor elimination pathway for dolutegravir with less than 1% of active drug excreted by the kidney.<sup>10</sup> As a result, dosage adjustments are not recommended for patients with renal insufficiency.<sup>26</sup> However, dosage adjustment recommendations for patients receiving dialysis cannot be made because PK data are not available for this population. Dolutegravir is an inhibitor of the renal transport protein organic cation transporter 2 (OCT2) and can result in a mild, benign, and reversible elevation in serum creatinine (10–14%).<sup>27, 42</sup> However, OCT2 inhibition can lead to potential drug interactions between dolutegravir and OCT2 substrates. For example, dofetilide is an OCT2 substrate with a very narrow therapeutic window, and caution is therefore warranted with dolutegravir coadministration. Other common OCT2 substrates that interact with dolutegravir

include metformin, cimetidine, triamterene, and procainamide.<sup>27</sup>

Dolutegravir is also a substrate for P-glycoprotein and human breast cancer resistance protein, two transporters that impair intestinal absorption and central nervous system (CNS) penetration of antiretroviral agents.<sup>27</sup> However, dolutegravir also has a high intrinsic passive membrane permeability that attenuates the effect of these transporters, allowing for rapid intestinal absorption ( $T_{\max}$  = 1–2 hours) and distribution to the CNS. In a 16-week open-label study of 13 ART-naïve patients receiving dolutegravir, abacavir, and lamivudine, dolutegravir concentrations in cerebrospinal fluid were similar to unbound plasma levels and exceeded 50% inhibitory concentrations.<sup>43</sup> Nearly all patients demonstrated evidence of viral suppression in both the plasma and cerebrospinal fluid (85%) in response to the ART regimen by week 16, which suggests a possible role for dolutegravir in the management of HIV-associated neurocognitive disorder.

Dolutegravir also achieves meaningful concentrations in anatomic sites linked to HIV transmission including the genital tract and colorectum.<sup>44</sup> Currently, these data are limited to a small group of healthy volunteers (8 women, 12 men), but support the evaluation of dolutegravir in HIV prevention and preexposure prophylaxis.

## Clinical Trials

### Treatment-Naïve Patients

The safety and efficacy of dolutegravir-based ART regimens in treatment-naïve adults have been compared with efavirenz-based and raltegravir-based regimens, two preferred regimens recommended by the DHHS treatment guidelines.<sup>1, 12–16</sup>

### Dolutegravir versus Efavirenz

The efficacy and safety of dolutegravir as part of an ART regimen was first evaluated in SPRING-1, a phase IIb randomized, multicenter, dose-ranging study of 205 treatment-naïve adults (86% were male).<sup>12</sup> Patients were randomly assigned (1:1:1:1) to efavirenz 600 mg/day ( $n$  = 50) or dolutegravir 10 mg ( $n$  = 53), 25 mg ( $n$  = 51), or 50 mg ( $n$  = 51) once/day. Investigators and participants were blinded to drug doses but were aware of the drug assignment. In

addition to the study drug, patients received an open-label nucleos(t)ide reverse transcriptase inhibitor (NRTI) background regimen of either tenofovir/emtricitabine (67%) or abacavir/lamivudine (33%) at the investigator's discretion. Inclusion criteria included a baseline HIV RNA of at least 1000 copies/ml and a CD4<sup>+</sup> cell count of at least 200 cells/mm<sup>3</sup>. The mean baseline HIV RNA levels and CD4<sup>+</sup> cell counts ranged from 4.4–4.6 log<sub>10</sub> copies/ml and from 309–334 cells/mm<sup>3</sup>, respectively.

The primary end point of SPRING-1 was virologic suppression at week 48, defined as an HIV RNA level below 50 copies/ml. Dolutegravir and efavirenz had similar rates of virologic suppression (90% and 82%, respectively). Dolutegravir achieved virologic suppression more quickly than efavirenz; by week 4, 66% of patients who received dolutegravir, regardless of dose, had virologic suppression versus 18% of efavirenz-treated patients.<sup>12</sup> Although rapid virologic suppression has been reported with other INSTIs, the clinical significance of this response is not known.<sup>45, 46</sup> Median CD4<sup>+</sup> cell counts for dolutegravir (+231 cells/mm<sup>3</sup>) and efavirenz (+174 cells/mm<sup>3</sup>) were similar ( $p$ =0.076). Rates of sustained virologic suppression through week 96 were similar for dolutegravir 10 mg (79%), 25 mg (78%), and 50 mg (88%) and efavirenz (72%). Both drugs achieved a comparable median increase in CD4<sup>+</sup> cell counts from baseline (+338 vs +301 cells/mm<sup>3</sup>, respectively;  $p$ =0.155).<sup>13</sup>

The SINGLE study was a randomized, controlled, multicenter, double-blind, double-dummy, noninferiority phase III trial that compared the efficacy and safety of dolutegravir and efavirenz in 833 ART-naïve adults.<sup>14</sup> Patients were randomized to receive either of two single-tablet once/day regimens: dolutegravir 50 mg/abacavir 600 mg/lamivudine 300 mg ( $n$  = 414) or efavirenz 600 mg/tenofovir 300 mg/emtricitabine 200 mg ( $n$  = 419). Most patients were white (68%) and male (84%). The median baseline HIV RNA level was 4.7 log<sub>10</sub> copies/ml in both treatment groups, and the median baseline CD4<sup>+</sup> cell counts were 335 cells/mm<sup>3</sup> for dolutegravir and 339 cells/mm<sup>3</sup> for efavirenz. The primary end point was the proportion of patients who achieved an HIV RNA level below 50 copies/ml by week 48. After confirming noninferiority, a prespecified superiority test demonstrated that more patients treated with dolutegravir versus efavirenz achieved the primary end point (88% vs 81%,  $p$ =0.003). As in SPRING-1, dolutegravir

was associated with a shorter time to virologic suppression (median 28 days) versus efavirenz (median 84 days,  $p < 0.0001$ ). Dolutegravir treatment also led to significantly greater median increases in CD4<sup>+</sup> cell count than efavirenz (+267 vs +208 cells/mm<sup>3</sup>, respectively;  $p < 0.001$ ). Although multiple different agents have been shown to be noninferior to efavirenz/tenofovir/emtricitabine, dolutegravir is the first antiretroviral found to be superior to efavirenz in treatment-naïve patients. This finding may be attributed to the different discontinuation rates due to adverse events between dolutegravir and efavirenz (2% vs 10%, respectively;  $p$  value not reported). Safety is discussed in depth in the following section. The discontinuation rate of efavirenz (10%) in the SINGLE study was higher than seen (5–6%) in other phase III clinical trials that compared efavirenz and INSTIs in treatment-naïve patients.<sup>45, 46</sup> Therefore, the superiority of dolutegravir over efavirenz should be carefully considered and applied because additional clinical data are needed to validate this finding.

#### *Dolutegravir versus Raltegravir*

The SPRING-2 study was a 96-week phase III, randomized, double-blind, active-controlled, noninferiority trial that compared the efficacy and safety of dolutegravir and raltegravir in 822 treatment-naïve adults.<sup>15</sup> Patients were randomized to receive dolutegravir 50 mg once/day ( $n = 411$ ) or raltegravir 400 mg twice/day ( $n = 411$ ). The background regimen consisted of either coformulated tenofovir/emtricitabine or abacavir/lamivudine, chosen at the investigator's discretion. A baseline HIV RNA level of at least 1000 copies/ml was required for study entry. There were no CD4<sup>+</sup> entry criteria; however, patients with active CDC category C disease (except Kaposi sarcoma) were excluded. The median baseline HIV RNA levels and CD4<sup>+</sup> cell counts were similar between the dolutegravir (4.52 log<sub>10</sub> copies/ml, 359 cells/mm<sup>3</sup>) and raltegravir groups (4.58 log<sub>10</sub> copies/ml, 362 cells/mm<sup>3</sup>). Most patients were white (86%) men (85%). Tenofovir/emtricitabine was more commonly used as the dual NRTI in both groups (60%). After 48 weeks, 88% of patients in the dolutegravir arm achieved an HIV RNA level below 50 copies/ml, compared with 85% in the raltegravir arm (adjusted difference, −2.5%, 95% confidence interval [CI] −2.2 to 7.1), meeting the criteria for noninferiority. The CD4<sup>+</sup> cell

counts increased by a median of 230 cells/mm<sup>3</sup> in both groups. Virologic suppression was similar between the two groups regardless of backbone dual NRTI or baseline HIV RNA level (100,000 or lower, or above 100,000 copies/ml). Although the 96-week data have not been published, preliminary data show that dolutegravir remained noninferior to raltegravir in terms of virologic suppression (81% vs 76%, respectively; adjusted difference 4.5%, 95% CI −1.1 to 10%). The increase in CD4<sup>+</sup> cell counts was similar between both groups (+276 vs +264,  $p$  value not reported).<sup>16</sup>

#### *Limitations*

The SINGLE and SPRING-2 studies showed the efficacy of dolutegravir in treatment-naïve patients, including its superiority over efavirenz.<sup>14, 15</sup> However, several limitations should be noted. Both studies enrolled predominately white men; therefore, more clinical data is needed in HIV-infected women and minorities. It is not anticipated that gender or race affects the PK properties of dolutegravir. In the SINGLE study, efavirenz and dolutegravir had similar rates of virologic suppression in terms of baseline HIV RNA level (100,000 or below or above 100,000 copies/ml) or CD4<sup>+</sup> cell count (200 or below or above 200 cells/mm<sup>3</sup>).<sup>14</sup> The SPRING-2 study demonstrated comparable rates of virologic suppression with respect to baseline HIV RNA level.<sup>15</sup> The application of this data is limited because both studies primarily enrolled patients with HIV RNA levels 100,000 or below copies/ml (68–72%) and few patients (13–14%) with advanced HIV disease (CD4<sup>+</sup> cell count 200 cells/mm<sup>3</sup> or below). Therefore, additional clinical data are needed in treatment-naïve patients with very low CD4<sup>+</sup> cell counts and high baseline HIV RNA levels.

Tenofovir/emtricitabine is the preferred dual NRTI backbone of ART regimens for treatment-naïve patients.<sup>1</sup> The SINGLE and SPRING-2 studies used tenofovir/emtricitabine and abacavir/lamivudine.<sup>14, 15</sup> In the SINGLE study, dolutegravir was coformulated with abacavir/lamivudine to create a single-tablet regimen; SPRING-2 allowed open-label use of either dual NRTI combination. The DHHS guidelines list abacavir/lamivudine as an alternative choice because of conflicting data regarding its virologic efficacy. The ACTG5202 study observed a shorter time to virologic failure with abacavir/lamivudine compared with tenofovir/emtricitabine in patients with a baseline HIV

RNA level above 100,000 copies/ml.<sup>47</sup> Additionally, abacavir/lamivudine was less likely to achieve virologic suppression compared with tenofovir/emtricitabine in the ASSERT study, although this may be due to the higher than expected discontinuation rate in the abacavir/lamivudine arm.<sup>48</sup> In contrast to the previous two studies, the HEAT study showed comparable rates of virologic suppression between tenofovir/emtricitabine and abacavir/lamivudine, regardless of baseline HIV RNA levels.<sup>49</sup> The SPRING-2 and SINGLE studies demonstrate that the efficacy of dolutegravir was comparable with raltegravir and efavirenz, respectively, regardless of which dual NRTI backbone was used.<sup>14, 15</sup>

### Treatment-Experienced Patients

Two studies have investigated the efficacy and safety of dolutegravir in treatment-experienced adults.<sup>17, 18</sup> The VIKING study was a phase IIb multicenter, open-label, single-arm pilot study that evaluated the effect of dolutegravir treatment in 51 patients who had virologic failure while taking raltegravir-containing regimens.<sup>17</sup> Patients received either dolutegravir 50 mg once/day ( $n = 27$ ) or twice/day ( $n = 24$ ) with the failing regimen (excluding raltegravir) for 10 days. After this functional monotherapy phase, background therapy was optimized using genotypic and phenotypic testing. Inclusion criteria were HIV RNA levels 1000 copies/ml or above, presence of genotypic INSTI resistance, and resistance to at least one medication from two different classes of ART (NRTIs, NNRTIs, PIs, or fusion/entry inhibitors). The primary end point was the proportion of patients who had HIV RNA below 400 copies/ml or at least a 0.7 log<sub>10</sub> copies/ml reduction in viral load on day 11. Although a rapid antiviral response was seen in both cohorts, more patients were likely to achieve the primary end point with twice/day dolutegravir by day 11 (96% vs 78%,  $p$  value not reported). Twice/day dosing also led to a significantly greater reduction in viral load compared with once/day dosing ( $-0.32$  log<sub>10</sub> copies/ml,  $p=0.017$ ). By week 24, the rate of virologic suppression was numerically higher with twice/day dosing (75% vs 41%,  $p$  value not reported). Immunologic recovery was similar for both groups (median increase of CD4<sup>+</sup> cells, +60 vs +54 cells/mm<sup>3</sup>, respectively;  $p$  value not reported). The VIKING study was the first to demonstrate the successful use of an

INSTI for the treatment of raltegravir-resistant HIV. However, because VIKING only enrolled 51 patients, larger studies are needed to clarify the role of dolutegravir in INSTI-resistant HIV. Two phase III trials are currently underway to evaluate twice/day dolutegravir for the treatment of raltegravir- or elvitegravir-resistant HIV.<sup>50, 51</sup>

Raltegravir and elvitegravir may be used as part of a salvage regimen in treatment-experienced patients with resistant HIV.<sup>1, 2, 52</sup> The SAILING study was a phase III randomized, double-blind, noninferiority trial that compared the safety and efficacy of dolutegravir with raltegravir in 715 treatment-experienced, INSTI-naïve patients.<sup>18</sup> Patients were enrolled if they had two consecutive HIV RNA levels of at least 400 copies/ml or above (or above 1000 copies/ml upon screening), resistance to two or more classes of ART medications, and were receiving one or two fully active drugs as background therapy. Patients were randomized 1:1 to receive either dolutegravir 50 mg once/day ( $n = 354$ ) or raltegravir 400 mg twice/day ( $n = 361$ ), along with optimized background therapy. Baseline HIV RNA levels were comparable for dolutegravir (4.17 log<sub>10</sub> copies/ml) and raltegravir (4.21 log<sub>10</sub> copies/ml). Additionally, baseline CD4<sup>+</sup> cell counts were similar between the two arms (204.5 vs 193 cells/mm<sup>3</sup>, respectively). Overall, 49% of patients had resistance to at least three drug classes, and 85% received background therapy that contained a ritonavir-boosted protease inhibitor.

The primary end point for SAILING was the proportion of patients achieving virologic suppression, defined as an HIV RNA level below 50 copies/ml at week 48.<sup>18</sup> Patients randomized to dolutegravir were significantly more likely to achieve virologic suppression (71% vs 64%,  $p=0.03$ ), which fulfilled the prespecified criteria for noninferiority and subsequent statistical superiority. CD4<sup>+</sup> cell counts increased from baseline in both groups (+162 vs +153 cells/mm<sup>3</sup>,  $p$  value not reported). Additionally, virologic failure due to treatment-emergent INSTI resistance was significantly less common with dolutegravir (adjusted difference  $-3.7\%$ ,  $p=0.003$ ).<sup>18</sup>

Based on the efficacy and safety demonstrated in phase III clinical studies in treatment-naïve and treatment-experienced patients (Tables 3 and 4), the U.S. Food and Drug Administration (FDA) approved dolutegravir for the treatment of HIV in adults.<sup>26</sup>

Table 3. Phase III clinical trials of dolutegravir<sup>14, 15, 18</sup>

| Study    | Design              | Patients              | Enrollment | Intervention                                                                                                                | Duration | Virologic suppression | Adjusted difference (95% CI) | CD4 <sup>+</sup> median increase | p Value |
|----------|---------------------|-----------------------|------------|-----------------------------------------------------------------------------------------------------------------------------|----------|-----------------------|------------------------------|----------------------------------|---------|
| SINGLE   | RCT, noninferiority | Treatment naive       | 414        | DTG 50 mg/ABC 600 mg/3TC 300 mg/day<br>EFV 600 mg/TDF 300 mg/FTC 200 mg/day                                                 | 48 wks   | 88%                   | 7.4% <sup>c</sup> (2.5–12.3) | 267                              | < 0.001 |
| SPRING-2 | RCT, noninferiority | Treatment naive       | 419        | DTG 50 mg + (ABC/3TC or TDF/FTC) once/day <sup>a</sup><br>RAL 400 mg twice/day + (ABC/3TC or TDF/FTC once/day) <sup>a</sup> | 48 wks   | 81%                   | 2.5% (–2.2 to 7.1)           | 208                              | NR      |
| SAILING  | RCT, noninferiority | Treatment experienced | 411        | DTG 50 mg once/day + OBR <sup>b</sup><br>RAL 400 mg twice/day + OBR <sup>b</sup>                                            | 48 wks   | 85%                   | 7.4% <sup>d</sup> (0.7–14.2) | 230                              | NR      |

CI = confidence interval; RCT = randomized controlled trial; DTG = dolutegravir; ABC = abacavir; 3TC = lamivudine; EFV = efavirenz; TDF = tenofovir; FTC = emtricitabine; RAL = raltegravir; OBR = optimized background regimen.

<sup>a</sup>TDF/FTC (59.5%) was more commonly used in both arms as compared with ABC/3TC (40.5%).

<sup>b</sup>The most common component of the OBR was a boosted protease inhibitor (85%).

<sup>c</sup>Predetermined superiority test performed after meeting noninferiority; p value = 0.003.

<sup>d</sup>Predetermined superiority test performed after meeting noninferiority; p value = 0.03.

## Safety

The safety of dolutegravir has been evaluated in clinical trials involving treatment-naïve and treatment-experienced patients. No serious adverse events or discontinuations due to adverse events were noted in a phase IIa trial of once/day dolutegravir monotherapy (dose range 2–50 mg) in treatment-naïve patients.<sup>20</sup> The rate of drug-related adverse events that occurred in the dolutegravir group was comparable with the placebo group, and dose-dependent trends were not observed. The subsequent phase IIb trial, SPRING-1, compared the safety and efficacy of dolutegravir with efavirenz, each combined with either coformulated tenofovir/emtricitabine or abacavir/lamivudine.<sup>12</sup> After 48 weeks, the rates of drug-related adverse events were 43% for dolutegravir and 58% for efavirenz; rates of serious adverse events were 5% and 8%, respectively (p value not reported). Gastrointestinal disturbances (nausea, diarrhea) were most common with dolutegravir, and neuropsychiatric symptoms were most common with efavirenz. The mean increase from baseline low-density lipoprotein cholesterol was greater in the efavirenz group (16 mg/dl) than in the dolutegravir arm (0.6 mg/dl). There was a modest increase in baseline serum creatinine by week 1 in the dolutegravir group, which remained steady through week 16 and returned to baseline levels by week 48 as compared with the efavirenz group (+0.10 vs +0.01 mg/dl, respectively; p<0.001). The safety profile was sustained through week 96, with drug-related adverse events occurring less frequently in the dolutegravir arm (47% vs 62%, p value not reported).<sup>13</sup> Additionally, adverse effects leading to discontinuation were less common with dolutegravir (2% vs 10%, p value not reported).

The phase III SINGLE study that compared the safety and efficacy of dolutegravir/abacavir/lamivudine and efavirenz/tenofovir/emtricitabine demonstrated similar findings in favor of dolutegravir.<sup>14</sup> Insomnia occurred more frequently with dolutegravir (15% vs 10%, p=0.029). Efavirenz was associated with a higher discontinuation rate due to adverse events (10% vs 2%, p value not reported). The most common reasons for discontinuation in the dolutegravir and efavirenz groups, respectively, were neuropsychiatric effects (7% vs less than 1%), gastrointestinal symptoms (2% vs 0%), and dermatologic reactions (2% vs less than 1%).

The phase III SPRING-2 study compared the safety and efficacy of dolutegravir and raltegravir

Table 4. Adverse events and select laboratory abnormalities associated with dolutegravir in phase III clinical trials<sup>14, 15, 18</sup>

|                                                         | SINGLE                    |                        | SPRING-2                  |                          | SAILING                   |                          |
|---------------------------------------------------------|---------------------------|------------------------|---------------------------|--------------------------|---------------------------|--------------------------|
|                                                         | Dolutegravir<br>(n = 414) | Efavirenz<br>(n = 419) | Dolutegravir<br>(n = 411) | Raltegravir<br>(n = 411) | Dolutegravir<br>(n = 354) | Raltegravir<br>(n = 361) |
| Adverse event, %                                        |                           |                        |                           |                          |                           |                          |
| Headache                                                | 13                        | 13                     | 12                        | 12                       | 9                         | 9                        |
| Dizziness                                               | 9                         | 35                     | 6                         | 6                        | —                         | —                        |
| Insomnia                                                | 15                        | 10                     | 5                         | 4                        | —                         | —                        |
| Abnormal dreams                                         | 7                         | 17                     | —                         | —                        | —                         | —                        |
| Nausea                                                  | 14                        | 14                     | 14                        | 13                       | 8                         | 8                        |
| Diarrhea                                                | 17                        | 18                     | 11                        | 11                       | 20                        | 18                       |
| Fatigue                                                 | 13                        | 12                     | 5                         | 4                        | 4                         | 7                        |
| Nasopharyngitis                                         | 15                        | 14                     | 11                        | 12                       | 11                        | 8                        |
| Discontinuation due to<br>adverse events, %             | 2                         | 10                     | 2                         | 1                        | 3                         | 4                        |
| Laboratory abnormalities, %                             |                           |                        |                           |                          |                           |                          |
| ALT $\geq 5 \times$ ULN                                 | < 1                       | < 1                    | 2                         | 2                        | 3                         | 2                        |
| Serum creatinine<br>Mean change from<br>baseline, mg/dl | + 0.11                    | 0                      | + 0.14                    | + 0.05                   | + 0.13                    | + 0.06                   |

ALT = alanine aminotransferase; ULN = upper limit of normal.

in treatment-naïve patients.<sup>15</sup> After 48 weeks, both INSTIs had a similar safety profile; the rates of serious adverse events in the dolutegravir and raltegravir arms were 7% and 8%, respectively. The most common adverse events in both groups were nausea, headache, nasopharyngitis, and diarrhea. Discontinuation rates due to serious adverse events were also low in the two arms. Three patients (less than 1%) in the dolutegravir arm and five patients (1%) in the raltegravir arm discontinued study medication for treatment-related adverse events. The mean change from baseline serum creatinine was +0.14 mg/dl for dolutegravir and +0.05 mg/dl for raltegravir; this difference between the two arms was not statistically significant. Additionally, there was no difference in the median change in the urine albumin-to-creatinine ratio, suggesting that the changes in serum creatinine were benign. This is consistent with data from PK studies of dolutegravir, which demonstrate that changes in serum creatinine and renal function are clinically insignificant.<sup>42</sup>

The phase IIb VIKING study investigated the safety and efficacy of dolutegravir 50 mg once/day or twice/day in treatment-experienced patients with documented raltegravir resistance.<sup>17</sup> At 24 weeks, adverse events of at least grade 2 severity occurred more frequently with twice/day (67%) as compared with once/day dosing (48%); however, no dose-related trends were observed with individual adverse events. In both groups, serum creatinine increased slightly from baseline within the first week and stabilized by week 4 (mean increase 0.14 mg/dl in both

arms). There were no study drug discontinuations in either group due to adverse events, including renal toxicity.

The phase III SAILING study compared dolutegravir and raltegravir in treatment-experienced patients.<sup>18</sup> Consistent with the results of SPRING-2, the rate of serious adverse events was similar in both groups at week 48 (9% vs 12%, respectively). The most common adverse events were diarrhea, upper respiratory tract infection, headache, and nausea. Both drugs were well tolerated, and discontinuation rates due to adverse events for both study drugs were infrequent (3% and 4%, respectively). Laboratory abnormalities were uncommon in both groups. Small, statistically insignificant increases in baseline serum creatinine were observed in the dolutegravir and raltegravir arms (+0.1 and +0.04 mg/dl, respectively; p value not reported).

Together, these clinical data demonstrate the favorable safety profile of dolutegravir. The most common adverse events are similar to raltegravir.<sup>38</sup> A small benign increase in serum creatinine was observed in clinical trials, due to inhibition of serum creatinine secretion by dolutegravir,<sup>42</sup> suggesting the need for initial monitoring to establish a new baseline serum creatinine within the first week of use. The safety profile for twice/day dolutegravir should be interpreted cautiously because the study enrolled only 24 patients in that arm.<sup>17</sup> Two additional phase III studies are underway in treatment-experienced patients that should further characterize the safety profile of twice/day dolutegravir in this patient population.<sup>50, 51</sup>

## Resistance

Resistance to INSTIs occurs with single-point mutations within the integrase gene. The three most common raltegravir mutations (N155H, Q148H/K/R, and Y143C/H/R) are associated with virologic failure and reduced susceptibility to raltegravir.<sup>53</sup> Continuing raltegravir in these patients may result in the development of additional mutations.<sup>54</sup> Moreover, if the virus harbors one or more of these mutations, cross-resistance between raltegravir and elvitegravir can occur.<sup>17</sup> An *in vitro* study demonstrated that dolutegravir has a higher genetic barrier to resistance than raltegravir and elvitegravir, which may be attributed to its significantly slower rate of dissociation (5–40 times slower) from the integrase enzyme in viruses that are either wild type or contain the N155, Q148, or Y143 mutations.<sup>55</sup> Additionally, dolutegravir may undergo slight conformational changes at the active site to overcome the physical barrier created by these single point mutations.<sup>56</sup> These data suggest that dolutegravir has limited cross-resistance to raltegravir and elvitegravir.<sup>17</sup>

No INSTI mutations were found in the SPRING-1 trial through 48 and 96 weeks.<sup>12, 13</sup> In SPRING-2, the virologic failure rate for dolutegravir was 5% compared with 8% for raltegravir.<sup>15</sup> There were no treatment-emergent INSTI or NRTI mutations in patients with virologic failure while taking dolutegravir. In contrast, virologic failure in patients who received raltegravir led to five treatment-emergent resistance mutations. Resistance to raltegravir ( $n = 1$ , 6%) and NRTIs ( $n = 4$ , 21%) was observed. In the SINGLE study, rates of virologic failure were identical between both arms (4%).<sup>14</sup> For patients with virologic failure and genotypic results in the dolutegravir arm ( $n = 9/18$ ), no INSTI or NRTI mutations were selected. Among the 17 patients with virologic failure in the efavirenz arm, 9 had genotypic results, and 5 mutations were identified (one NRTI [K65R] and four NNRTI mutations).

The VIKING study provided data about the effect of baseline raltegravir resistance on the development of dolutegravir resistance.<sup>17</sup> Virologic failure was more common with once/day ( $n = 12$ , 44%) versus twice/day dolutegravir dosing ( $n = 5$ , 21%). Treatment-emergent INSTI mutations occurred in 41% of patients (7 of 17) with virologic failure, five of whom had a virus with both the Q148 mutation and at least one additional raltegravir-associated mutation at

baseline. Phenotypic resistance at time of virologic failure, as measured by the fold increase in the 50% inhibitory concentration of dolutegravir, varied from 6.58–93. Although the most commonly acquired mutation was N155H, the greatest increase in dolutegravir fold-change occurred in patients with the Q148 mutation, whether the Q148H mutation was present at baseline or acquired during therapy.

The SAILING trial showed the difference in treatment-emergent integrase mutations between two INSTIs in treatment-experienced patients.<sup>18</sup> Dolutegravir had a significantly lower rate of virologic failure (4, 1.1%) with treatment-emergent INSTI mutations compared with raltegravir (17, 4.7%;  $p=0.003$ ).

These data demonstrate that dolutegravir has a higher genetic barrier to resistance compared with raltegravir in treatment-naïve and treatment-experienced patients who experience virologic failure. Based on preliminary clinical data from the VIKING study, twice/day dolutegravir is preferred in patients with INSTI resistance at baseline. Furthermore, the dolutegravir product labeling warns clinicians of the poor virologic response in patients who have the Q148 mutation plus two or more additional INSTI-related mutations.<sup>26</sup> Therefore, providers should perform genotypic and phenotypic resistance tests in treatment-experienced patients prior to the initiation of dolutegravir. Phase III studies that investigate the use of dolutegravir for treatment-experienced patients with raltegravir and/or elvitegravir resistance are underway and will provide much needed evidence to determine the place of dolutegravir in this patient population.<sup>50, 51</sup>

## Place in Therapy

Raltegravir is often used as part of an ART regimen for both treatment-naïve and treatment-experienced patients because it is effective in achieving virologic suppression, is well tolerated, and has limited drug–drug interactions.<sup>1–3</sup> One disadvantage is the need for twice/day dosing. Because patients prefer once/day regimens, specifically single-tablet regimens, a single-tablet regimen with another INSTI was developed.<sup>3–6</sup> This regimen, elvitegravir/cobicistat/tenofovir/emtricitabine, was recently approved for the management of treatment-naïve patients.<sup>7</sup> Like raltegravir, elvitegravir is well tolerated. However, to be administered once/day, raltegravir must be coadministered with the potent CYP3A4 inhibitor cobicistat, which can lead to clinically

significant drug–drug interactions with ART and other classes of medications.<sup>7, 9</sup> Dolutegravir combines the advantages of both first-generation INSTIs: it is well-tolerated and can be given once/day without the use of a booster, thus limiting the number of significant drug–drug interactions. Moreover, a single-tablet dolutegravir/abacavir/lamivudine regimen has been studied in a phase III trial and is being pursued for approval.<sup>11, 14</sup> The disadvantage of the dolutegravir single-tablet regimen, compared with other single-tablet regimens, is the required genetic screening for HLA-B\*5701, which is recommended prior to abacavir initiation.<sup>1</sup>

Clinical studies of dolutegravir in treatment-naïve and treatment-experienced patients have demonstrated its efficacy and safety.<sup>12–18</sup> Dolutegravir was the first ART found to be superior to efavirenz for treatment-naïve patients and to raltegravir for treatment-experienced patients. In addition, dolutegravir has a higher genetic barrier to resistance compared with raltegravir.<sup>15, 16, 18</sup> Early clinical data suggest that dolutegravir may be effective for patients that harbor raltegravir-resistant virus, and additional phase III studies are underway to further delineate its role in these patients.<sup>17, 50, 51</sup>

Although dolutegravir seems promising as a treatment option, many questions remain. Further studies are needed to compare the relative efficacy and safety with PI-based regimens; two are currently underway comparing dolutegravir with ritonavir-boosted atazanavir and darunavir in treatment-naïve patients.<sup>57, 58</sup> More clinical data are needed in HIV-infected women and minorities. A phase III study was recently initiated to determine the safety and efficacy of dolutegravir/abacavir/lamivudine as a single-tablet regimen specifically in treatment-naïve women.<sup>58</sup> Additional data are also needed in patients with advanced HIV because this population was not well represented in the phase III studies. Furthermore, although dolutegravir achieves adequate concentrations in the genital tract, no clinical trials are underway to determine its role in preexposure prophylaxis.<sup>44</sup> Lastly, dolutegravir was approved for use in pediatric patients (age 12 years or older weighing 40 kg or more) based on preliminary data from a phase I/II open-label study. This ongoing study is evaluating the safety and efficacy of dolutegravir in children, including younger patients (age 6 weeks–12 years).<sup>59</sup>

Dolutegravir was approved by the FDA in August 2013 for treatment-naïve and treatment-experienced patients.<sup>26</sup> In October 2013, the

DHHS added elvitegravir and dolutegravir as preferred agents for the management of treatment-naïve patients.<sup>8</sup> We believe that dolutegravir is a highly attractive option among the preferred agents for treatment-naïve and treatment-experienced patients because of its safety, efficacy, high genetic barrier to resistance, and anticipated availability as a single-tablet regimen.

## References

1. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, February 2013. Available from <http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf>. Accessed September 25, 2013.
2. Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med* 2008;359:339–54.
3. Rockstroh JK, Lennox JL, DeJesus E, et al. Long-term treatment with raltegravir or efavirenz combined with tenofovir/emtricitabine for treatment-naïve human immunodeficiency virus-1-infected patients: 156-Week results from STARTMRK. *Clin Infect Dis* 2011;53:807–816.
4. DeJesus E, Young B, Morales-Ramirez JO, et al. Simplification of antiretroviral therapy to a single-tablet regimen consisting of efavirenz, emtricitabine, and tenofovir disoproxil fumarate vs unmodified antiretroviral therapy in virologically suppressed HIV-1-infected patients. *J Acquir Immune Defic Syndr* 2009;51:163–74.
5. Sax PE, Meyers JL, Mugavero M, Davis KL. Adherence to antiretroviral treatment and correlation with risk of hospitalization among commercially insured HIV patients in the United States. *PLoS ONE* 2012;7:e31591.
6. Airolidi M, Zaccacelli M, Bisi L, et al. One-pill once-a-day HA-ART: a simplification strategy that improves adherence and quality of life of HIV-infected subjects. *Patient Prefer Adherence* 2010;4:115–25.
7. Gilead Sciences, Inc. Stribild (elvitegravir/cobicistat/tenofovir/emtricitabine) package insert. Foster City, CA; 2012.
8. Department of Health and Human Services. Recommendation on integrase inhibitor use in antiretroviral treatment-naïve HIV-infected individuals from the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Available from <http://aidsinfo.nih.gov/news/1392/hhs-panel-on-antiretroviral-guidelines-for-adults-and-adolescents-updates-recommendations-on-insti-based-regimens-for-art-naive-individuals>. Accessed October 31, 2013.
9. Shah BM, Schafer J, Priano J, Squires KE. Cobicistat: A new boost for the treatment of human immunodeficiency virus infection. *Pharmacotherapy* 2013;33:1107–16.
10. Min S, Song I, Borland J, et al. Pharmacokinetics and safety of S/GSK1349572, a next-generation HIV integrase inhibitor, in healthy volunteers. *Antimicrob Agents Chemother* 2010;54:254–258.
11. Viiv Healthcare. Our pipeline. Available from <http://www.viiv-healthcare.com/r-and-d/our-pipeline.aspx>. Accessed July 3, 2013.
12. van Lunzwn J, Maggiolo F, Arribas JR, et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naïve adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised phase 2b trial. *Lancet Infect Dis* 2012;12:111–8.
13. Stellbrink HJ, Reynes J, Lazzarin A, et al. Dolutegravir in antiretroviral-naïve adults with HIV-1: 96-week results from a randomized dose-ranging study. *AIDS* 2013;27:1771–8.
14. Walmsley S, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013;369:1807–18.

15. Raffi F, Rachlis A, Stellbrink HJ, et al. Once-daily dolutegravir vs raltegravir in antiretroviral-naïve adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. *Lancet* 2013;381:735–43.
16. Raffi F, Jaeger H, Motta D, et al. Dolutegravir is non-inferior to raltegravir and shows durable response through 96 weeks: results from the SPRING-2 trial [abstract TULBPE17]. 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention. Kuala Lumpur, Malaysia, June 30–July 3, 2013.
17. Eron JJ, Clotet B, Durant J, et al. Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. *J Infect Dis* 2013;207:740–8.
18. Cahn P, Pozniak AL, Mingrone H, et al. Dolutegravir vs raltegravir in antiretroviral-experienced, integrase-inhibitor-naïve adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. *Lancet* 2013;382:700–8.
19. Hazuda DJ, Iwamoto M, Wenning L. Emerging pharmacology: inhibitors of human immunodeficiency virus integration. *Annu Rev Pharmacol Toxicol* 2009;49:377–94.
20. Min S, Sloan L, DeJesus E, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults. *AIDS* 2011;25:1737–1745.
21. Iwamoto M, Wenning LA, Petry AS, et al. Safety, tolerability, and pharmacokinetics of raltegravir after single and multiple doses in healthy subjects. *Clin Pharmacol Ther* 2008;83:293–9.
22. Kawaguchi I, Ishikawa T, Ishibashi M, Irie S, Kakee A. Safety and pharmacokinetics of single oral dose of JTK-303/GS-9137, a novel HIV integrase inhibitor, in healthy volunteers (poster 580). In: Program and abstracts: the 13th Conference on Retroviruses and Opportunistic Infections. Denver, CO, 2006.
23. Markowitz M, Morales-Ramirez JO, Nguyen BY, et al. Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel integrase inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naïve HIV-1-infected individuals. *J Acquir Immune Defic Syndr* 2006;43:509–15.
24. DeJesus E, Berger D, Markowitz M, et al. Antiviral activity, pharmacokinetics, and dose response of the HIV-1 integrase inhibitor GS-9137 (JTK-303) in treatment naïve and treatment experienced patients. *J Acquir Immune Defic Syndr* 2006;43:1–5.
25. Wenning LA, Hwang E, Nguyen BY, et al. Pharmacokinetic/pharmacodynamics analyses for raltegravir in phase III studies in treatment-experienced HIV-infected patients following 48 weeks of treatment [abstract H-4054]. 48th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC, October 25–28, 2008.
26. ViiV Healthcare. Tivicay (dolutegravir) package insert. Research Triangle Park, NC; 2013.
27. Reese MJ, Savina PM, Generaux GT, et al. In vitro investigations into the roles of drug transporters and metabolizing enzymes in the disposition and drug interactions of dolutegravir, a HIV integrase inhibitor. *Drug Metab Dispos* 2013;41:353–361.
28. Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. *J Acquir Immune Defic Syndr* 2013;62:21–27.
29. Song I, Borland J, Chen S, et al. Effect of atazanavir and atazanavir/ritonavir on the pharmacokinetics of the next-generation HIV integrase inhibitor, S/GSK1349572. *Br J Clin Pharmacol* 2011;72:103–108.
30. Song I, Min SS, Borland J, et al. The effect of lopinavir/ritonavir and darunavir/ritonavir on the HIV integrase inhibitor S/GSK1349572 in healthy participants. *J Clin Pharmacol* 2011;51:237–242.
31. Song I, Borland J, Chen S, et al. Effect of fosamprenavir/ritonavir on the pharmacokinetics of the integrase inhibitor, dolutegravir, in healthy subjects [abstract A1-1727]. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, IL, September 17–20, 2011.
32. Song I, Borland J, Lou Y, et al. Effects of enzyme inducers, tipranavir and efavirenz, on the pharmacokinetics of the integrase inhibitor, dolutegravir (S/GSK1349572) [abstract O-02]. 12th International Workshop on Clinical Pharmacology of HIV Therapy. Miami, FL, April 13–15, 2011.
33. Ford SL, Gould E, Chen S, et al. Lack of pharmacokinetic (PK) interaction between rilpivirine and the integrase inhibitors dolutegravir and S/GSK1265744 [abstract A-1249]. 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, CA, September 9–12, 2012.
34. Song I, Min SS, Borland J, et al. Lack of interaction between the HIV integrase inhibitor S/GSK1349572 and tenofovir in healthy subjects. *J Acquir Immune Defic Syndr* 2010;55:365–67.
35. Song I, Borland J, Min S, et al. Effects of etravirine alone and with ritonavir-boosted protease inhibitors on the pharmacokinetics of dolutegravir. *Antimicrob Agents Chemother* 2011;55:3517–3521.
36. Song I, Mark S, Borland J, et al. Dolutegravir has no effect on the pharmacokinetics of methadone or oral contraceptives with norgestimate and ethinyl estradiol [abstract 535]. 20th Conference on Retroviruses and Opportunistic Infections. Atlanta, GA, March 3–6, 2013.
37. Johnson M, Borland J, Chen S, et al. The effect of boceprevir and telaprevir on dolutegravir pharmacokinetics in healthy adult subjects [abstract O\_07]. 14th International Workshop on Clinical Pharmacology of HIV Therapy. Amsterdam, the Netherlands, April 22–24, 2013.
38. Merck, Inc. Isentress (raltegravir) package insert. Whitehouse Station, NJ; 2013.
39. Song I, Borland J, Chen S, et al. Effect of food on the pharmacokinetics of the integrase inhibitor, dolutegravir. *Antimicrob Agents Chemother* 2011;56:1627–1629.
40. Patel P, Song I, Borland J, et al. Pharmacokinetics of the HIV integrase inhibitor S/GSK1349572 co-administered with acid-reducing agents and multivitamins in healthy volunteers. *J Antimicrob Chemother* 2011;66:1567–1572.
41. Song I, Borland J, Savina P, et al. Pharmacokinetics of dolutegravir in subjects with moderate hepatic impairment [abstract 608]. 19th Conference on Retroviruses and Opportunistic Infections. Seattle, WA, March 5–8, 2012.
42. Koteff J, Borland J, Chen S, et al. A phase 1 study to evaluate the effect of dolutegravir on renal function via measurement of iohexol and para-aminohippurate clearance in healthy subjects. *Br J Clin Pharmacol* 2012;75:990–996.
43. Letendre S, Mills A, Tashima K, et al. Distribution and antiviral activity in cerebrospinal fluid (CSF) of the integrase inhibitor, dolutegravir (DTG):ING116070 week 16 results [abstract 178LB]. 20th Conference on Retroviruses and Opportunistic Infections. Atlanta, GA, March 3–6, 2013.
44. Greener BN, Adams JL, Patterson KB, et al. Single and multiple dose dolutegravir pharmacokinetics in the genital tract and colorectum of HIV negative men and women [abstract 531]. 20th Conference on Retroviruses and Opportunistic Infections. Atlanta, GA, March 3–6, 2013.
45. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based vs efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet* 2009;374:796–806.
46. Sax PE, DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir vs co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet* 2012;379:2439–48.
47. Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine vs tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med* 2009;361:2230–2240.
48. Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine vs tenofovir/emtricitabine, administered with

- efavirenz, in antiretroviral-naïve, HIV-1-infected adults: 48-week results from the ASSERT study. *J Acquir Immune Defic Syndr* 2010;55:49–57.
49. Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS* 2009;23:1547–1556.
  50. ViiV Healthcare. Study assessing dolutegravir in HIV-1 infected subjects with virus resistant to raltegravir and/or elvitegravir (VIKING-4). ClinicalTrials.gov. Bethesda, MD: National Library of Medicine. Available from <http://clinicaltrials.gov/ct2/show/NCT01568892?term=dolutegravir+raltegravir&rank=1>. NLM identifier: NCT01568892. Accessed July 3, 2013.
  51. ViiV Healthcare. A study to assess dolutegravir in HIV-infected subjects with treatment failure on an integrase inhibitor containing regimen (VIKING-3). ClinicalTrials.gov. Bethesda, MD: National Library of Medicine. Available from <http://clinicaltrials.gov/ct2/show/NCT01328041?term=dolutegravir+raltegravir&rank=3>. NLM identifier: NCT01328041. Accessed July 3, 2013.
  52. Molina JM, Lamarca A, Andrade-Vilanova J, et al. Efficacy and safety of once daily elvitegravir vs twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. *Lancet Infect Dis* 2012;12:27–35.
  53. Cooper DA, Steigbigel RT, Gatell JM, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. *N Engl J Med* 2008;359:355–65.
  54. Mbisa JL, Martin SA, Cane PA. Patterns of resistance development with integrase inhibitors in HIV. *Infect Drug Resist* 2011;4:65–76.
  55. Hightower KE, Wang R, DeAnda F, et al. Dolutegravir (S/GSK1349572) exhibits significantly slower dissociation than raltegravir and elvitegravir from wild-type and integrase inhibitor-resistant HIV-1 integrase-DNA complexes. *Antimicrob Agents Chemother* 2011;55:4552–9.
  56. Hare S, Smith SJ, Métifiot M, et al. Structural and functional analyses of the second-generation integrase strand transfer inhibitor dolutegravir (S/GSK1349572). *Mol Pharmacol* 2011;80:565–72.
  57. ViiV Healthcare. Dolutegravir compared to darunavir/ritonavir, each in combination with dual nucleoside reverse transcriptase inhibitors (NRTIs) in ART-naïve subjects (FLAMINGO). ClinicalTrials.gov. Bethesda, MD: National Library of Medicine. Available from <http://clinicaltrials.gov/ct2/show/NCT01449929?term=dolutegravir&rank=10>. NLM identifier: NCT01449929. Accessed July 3, 2013.
  58. ViiV Healthcare. A study to determine safety and efficacy of dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) in human immunodeficiency virus (HIV)-1 infected antiretroviral therapy (ART) naïve women (ARIA). ClinicalTrials.gov. Bethesda, MD: National Library of Medicine. Available from <http://clinicaltrials.gov/ct2/show/NCT01910402?term=dolutegravir&rank=16>. NLM identifier: NCT01910402. Accessed September 25, 2013.
  59. ViiV Healthcare. Safety of and immune response to GSK1349572 in HIV-1 infected infants, children, and adolescents. ClinicalTrials.gov. Bethesda, MD: National Library of Medicine. Available from <http://clinicaltrials.gov/ct2/show/NCT01302847?term=GSK1349572+infant&rank=1>. NLM identifier: NCT01302847. Accessed September 25, 2013.