Dolutegravir: A Next-Generation Integrase Inhibitor for Treatment of HIV Infection

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Dolutegravir (DTG), a next-generation integrase strand transfer inhibitor (INSTI), was recently approved for use in the treatment of human immunodeficiency virus infection. In treatment-naive trial participants, DTG given at 50 mg once daily without pharmacologic boosting combined with a standard nucleoside backbone was shown to be noninferior or superior to first-line regimens containing efavirenz, darunavir/ritonavir, or raltegravir regardless of pretreatment viral load. This drug also exhibited efficacy in antiretroviral therapy–experienced participants and has proven to retain activity when dosed twice daily in some participants harboring resistance to the other INSTIs, raltegravir and elvitegravir. DTG has few drug interactions and is taken without regard to meals. It causes benign elevations in serum creatinine based on its inhibition of tubular creatinine secretion without affecting the glomerular filtration rate. Overall, DTG is well tolerated, with headache and insomnia being the most frequently reported adverse events.

Keywords. dolutegravir; integrase; HIV; resistance; INSTI.

Advances in antiretroviral therapy (ART) have markedly improved the prognosis of human immunodeficiency virus (HIV) infection; however, with increasing survival comes the need for new drugs that are well tolerated, efficacious, and durable and that can salvage prior treatment failures [1, 2]. In 2007, the first integrase strand transfer inhibitor (INSTI), raltegravir (RAL), was approved by the US Food and Drug Administration (FDA) after studies showed it to be efficacious in both ART-naive and -experienced participants when dosed twice daily [2, 3]. The next INSTI, elvitegravir (EVG), was approved in 2012 as part of a fixed-dose daily tablet containing tenofovir (TDF), emtricitabine (FTC), and the cytochrome P450 isoenzyme 3A (CYP3A) inhibitor cobicistat [4,5]. However, EVG is not manufactured as a stand-alone agent and requires pharmacologic boosting to be given once daily. In addition, significant cross-resistance between RAL and EVG prevents sequential therapy with these 2 drugs [6, 7]. Recently, the FDA approved dolutegravir (DTG) as the newest INSTI for treatment of HIV in ART-naive and -experienced persons based on studies demonstrating efficacy and safety. The drug has advantages over prior INSTIs in that it can be given once daily without boosting and can overcome some prior INSTI failures. We review the pharmacologic properties, drug interactions, in vitro activity, resistance, and clinical trial and adverse event data for this new agent.

PHARMACOKINETICS

The pharmacokinetic profile, safety, and tolerability of DTG were studied in healthy volunteers in a single- and multiple-dose escalation trial using doses of 2–100 mg/day [8]. The drug was readily absorbed and exhibited a half-life of 13–15 hours. Clinical studies indicate that DTG is primarily metabolized via hepatic glucuronidation by UDP-glucuronosyltransferase (UGT) 1A1 with a small contribution from CYP3A4 [9]. The drug was evaluated at a dose of 50 mg daily in HIV-negative participants with severe renal impairment...
(creatinine clearance <30 mL/minute) and, whereas the DTG maximum plasma concentration and area under the plasma concentration–time curve were 23% and 40% lower, respectively, than in the healthy controls, these changes were not thought to be clinically significant [10]. Although no adjustment for renal failure is recommended, DTG has not been studied in patients requiring dialysis. Caution is advised by the manufacturer when administering DTG to patients with INSTI resistance and severe renal failure, as subtherapeutic levels could occur, leading to further development of resistance or lack of efficacy [11]. Dolutegravir 50 mg was also studied in healthy volunteers in a single-dose crossover study in the fasted state or with low-, moderate-, or high-fat meals [12]. Food increased DTG exposure moderately compared with fasting, but is not thought to impact safety or toxicities. Patients with severe hepatic impairment (Child-Pugh class C) were excluded from clinical trials; however, there is no evidence of impaired metabolism when studied in those with mild to moderate liver disease despite DTG being metabolized primarily by the liver [13].

**DRUG INTERACTIONS**

Because DTG is primarily metabolized by UGT1A1 with a contribution from CYP3A, drugs that either induce or inhibit these enzymes could affect DTG levels. A study of DTG combined with the nonnucleoside reverse transcriptase inhibitor etravirine (ETR) significantly reduced exposure to DTG, such that DTG and ETR should not be combined alone [14]. However, in the second part of this study, coadministration of the protease inhibitors darunavir/ritonavir (DRV/RTV) or lopinavir/ritonavir (LPV/RTV) with ETR and DTG mitigated this effect. Therefore, DTG can be taken with ETR when combined with one of these boosted protease inhibitors. Atazanavir/RTV increases DTG levels as well and is expected to overcome this effect of ETR [15]. Other drugs that are potent CYP3A4 enzyme inducers, such as efavirenz (EFV), fosamprenavir/(RTV), tipranavir/(RTV), and rifampin, decrease DTG levels and require a DTG dose adjustment to 50 mg twice daily in treatment-naive and treatment-experienced, INSTI-naive participants [16–18]. In those with suspected or proven INSTI resistance, selection of other noninducing antiretrovirals in combination with DTG is suggested by the manufacturer [11]. Other metabolic inducers such as nevirapine, oxcarbazepine, phenytoin, phenobarbital, carbamazepine, and St John’s wort are not recommended to be given with DTG, as there are insufficient data to make dosing recommendations [11]. DRV/RTV, LPV/RTV, rilpivirine, TDF, boceprevir, telaprevir, prednison, rifabutin, and omeprazole have no clinically significant effect on the pharmacokinetics of DTG [18–23]. Absorption of DTG does not appear to be pH dependent; however, DTG should not be simultaneously administered with cation-containing antacids [24]. The activity of DTG is dependent on binding to magnesium ions located at the catalytic site of the integrase enzyme to prevent viral DNA transfer into the host genome, and chelation with these products is possible. If combined, DTG should be administered 2 hours before or 6 hours after taking medications containing polyvalent cations [24]. Multivitamins with iron had no clinically significant effect on DTG drug levels [24]. Dolutegravir inhibits the renal organic cation transporter OCT2 in vitro and may increase plasma concentrations of drugs eliminated via OCT2, such as the antiarrhythmic dofetilide and metformin. Otherwise, it appears that DTG will have little effect on the metabolism of other drugs such as methadone or oral contraceptives [25, 26].

**IN VITRO ACTIVITY AND RESISTANCE**

Dolutegravir exerts its antiviral activity by inhibiting HIV type 1 (HIV-1) integrase-catalyzed strand transfer into host cell DNA [27]. The mechanism of action of DTG has been established through several measurements including in vitro integrase enzyme assays, resistance passage experiments, and mechanistic cellular assays [27]. Multiple passage experiments performed with wild-type HIV-1 in culture in the presence of DTG and RAL showed >5-fold reduced susceptibility measured via phenotype to RAL by day 28. In contrast, no highly resistant mutants were isolated in the presence of DTG at day 112, indicating that DTG has a higher barrier to the development of resistance than RAL [27]. There are 3 primary mutation pathways described for RAL: Y143CHR, Q148HKR, and N155H [28]. High-level resistance to EVG has been associated with the selection of T66I, E92Q, Q146P, and S147G. An accumulation of other secondary mutations has been associated with failure of both drugs [7]. Unfortunately, there is significant cross-resistance between RAL and EVG [6, 7]. In vitro as well as clinical data indicate that HIV-1 with primary mutations at codon 155 or 143, and the T66I and E92Q mutants remain susceptible to DTG, whereas mutations at codon 148 in the presence of other secondary mutations can lead to decreased DTG efficacy [29, 30]. In a subanalysis of cohort II of the VIKING study, participants with current or historic RAL failure with triple-class resistance (including INSTI) received DTG 50 mg twice daily in addition to their failing regimen (functional monotherapy phase) for 10 days, then DTG plus an optimized background regimen (OBR). Twelve of 13 participants with baseline Y143 and N155 mutations achieved HIV-1 RNA (viral load [VL]) <400 copies/mL at week 24, whereas 8 of 11 participants with Q148 plus ≥1 additional RAL-associated mutation achieved a VL <400 copies/mL at week 24 [30]. In the VIKING-3 trial, 183 patients with RAL and/or EVG-resistant virus plus resistance to ≥2 other ART classes received open-label DTG 50 mg twice daily while continuing their failing regimen.
Dolutegravir was evaluated in SPRING-1, a 96-week, randomized, dose-ranging study in treatment-naive HIV-1–infected individuals who received DTG 10, 25, or 50 mg once daily or EFV 600 mg once daily combined with an investigator-selected nucleoside reverse transcriptase inhibitor (NRTI) background regimen of TDF/FTC or abacavir (ABC)/lamivudine (3TC). Through week 96, 72% of the participants in the EFV arm vs 79%, 78%, and 88% in the DTG 10, 25, and 50 mg arms, respectively, were responders via the FDA time to loss of virologic response algorithm with VL <50 copies/mL [31, 34]. No participants on DTG who met the definition for virologic failure (VF) had emergence of an INSTI mutation. The virologic response seen in the DTG 50 mg arm with improved tolerability compared with EFV led to further study of DTG at this dose [35].

Three additional trials were performed comparing DTG 50 mg daily with other first-line ART in naive participants. In SINGLE, a double-blind randomized controlled trial (RCT) in 833 ART-naive adults with no baseline resistance, DTG 50 mg daily plus ABC/3TC once daily was compared with the fixed-dose combination of TDF/FTC/EFV daily. At week 48, 88% of the participants receiving DTG had VL <50 copies/mL via the FDA snapshot algorithm vs 81% in the EFV arm (P = .003), meeting the criteria for superiority [36]. These results were maintained across subgroups including those with baseline VL < or ≥100 000 copies/mL. The median time to virologic suppression (VL <50 copies/mL) was 28 days in the DTG arm vs 84 days in the EFV arm (nominal P < .001), highlighting DTG’s ability to rapidly decrease VL. Of note, no emergent INSTI mutations were reported in those with VF in the DTG arm. Dolutegravir was also compared with DRV/RTV plus an investigator-selected NRTI backbone of ABC/3TC or TDF/FTC in an open-label RCT (FLAMINGO) in 484 naive adults, in whom 90% and 83%, respectively, achieved VL <50 copies/mL at 48 weeks via the FDA snapshot algorithm (P = .025) [37]. A higher response rate to DTG emerged in those participants with baseline VL >100 000 copies/mL (93% vs 70% with DRV/RTV). There was no difference based on NRTI backbone. Two participants in each arm experienced VF and none of them had emergence of resistance. Dolutegravir superiority was due to fewer withdrawals in the DTG arm related to adverse events and efficacy in those with VL >100 000 copies/mL. Finally, in an ongoing RCT (SPRING-2), 822 ART-naive participants were randomized to DTG 50 mg daily or RAL 400 mg twice daily plus an investigator-selected NRTI backbone of either ABC/3TC or TDF/FTC [38]. At week 96, 81% in the DTG arm and 76% in the RAL arm by the FDA snapshot algorithm had VL <50 copies/mL confirming noninferiority. Consistent with other studies, no patient had emergent INSTI resistance while failing DTG; however, 1 patient in the RAL arm developed an INSTI mutation and 4 developed NRTI mutations [39].

Both RAL and DTG were well tolerated (Table 1).

Dolutegravir demonstrated efficacy in 3 trials of its use in ART-experienced participants, including those with resistance to RAL and EVG. The first is SAILING, a 48-week, placebo-controlled trial in 715 ART-experienced, INSTI-naive participants with resistance to ≥2 classes of ART and 1–2 fully active agents available for background therapy. Participants were randomized to receive DTG 50 mg once daily or RAL 400 mg twice daily plus an investigator-selected OBR. At week 48, 71% of the participants on DTG and 64% of the participants on RAL had VL <50 copies/mL per the FDA snapshot algorithm, indicating superiority (P = .003) [40]. The difference in response was driven by virologic outcomes, as discontinuations and adverse event rates were similar between the 2 groups. When stratified by VL ≥50 000 copies/mL, DTG did better than RAL at achieving viral suppression (62% vs 47%, difference 15.2% [95% confidence interval, 1.9–28.4]). Fewer participants in the DTG arm with VF had treatment-emergent genotypic or phenotypic INSTI resistance by week 48 (4 [1%] for DTG vs 17 [5%] for RAL; P = .003). One patient in each arm had primary RAL resistance at baseline despite being INSTI naive (DTG arm: 148H/140S pathway; RAL arm: 143 pathway). Three participants in the DTG arm with emergent INSTI mutations experienced a <2-fold change in phenotypic susceptibility to both DTG and RAL, calling into question the clinical significance of the mutations. RAL-associated significant genotypic resistance was demonstrated in 42% of the participants with VF in the RAL arm but conferred limited cross-resistance to DTG [40]. This concept was studied further in VIKING, an open-label, single-arm pilot study with 2 sequential cohorts of HIV-1–infected adults failing their current regimen with current or historic RAL treatment failure, evidence of RAL resistance at screening, and resistance in ≥1 other ART class [41]. The 50 mg once-daily
dose of DTG was initially selected for evaluation in cohort I (n = 27); however, the suboptimal viral load response in some participants prompted an amendment to the protocol, and the dose was increased to 50 mg twice daily in cohort II (n = 24). The treatment phase for both cohorts involved a 10-day functional monotherapy period, where the participants were given DTG plus their currently failing ART (minus RAL), followed by a second phase from day 11 to 24 weeks where they were given DTG plus an investigator-selected OBR. In cohort I, it was suggested that participants have ≥1 active agent in the OBR, but it was mandated for cohort II. The primary efficacy endpoint was the proportion of participants on day 11 with a VL <400 copies/mL or a drop of ≥0.7 log_{10} copies/mL below the baseline value. In cohort I, 78% of the

### Table 1. Major Comparative Studies of Dolutegravir in Antiretroviral-Naive Participants

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Comparator</th>
<th>No. of Participants</th>
<th>Virologic Efficacy, %</th>
<th>No. Stopped Due to AE^a</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b EFV</td>
<td>50</td>
<td>53^b</td>
<td>72 vs 79^c</td>
<td>5 vs 4</td>
<td>SPRING-1 [35, 39]</td>
</tr>
<tr>
<td>2b</td>
<td>51^d</td>
<td>72 vs 78^c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 EFV</td>
<td>419</td>
<td>414^a</td>
<td>81 vs 88^f [AD, 7% [CI, 2%–12%]]</td>
<td>42 vs 10</td>
<td>SINGLE [36]</td>
</tr>
<tr>
<td>3</td>
<td>242</td>
<td>242^g</td>
<td>83 vs 90^j [AD, 7.1% [CI, 9%–13.2%]]</td>
<td>9 vs 3</td>
<td>FLAMINGO [37]</td>
</tr>
<tr>
<td>3 RAL</td>
<td>411</td>
<td>411^h</td>
<td>76 vs 81^i [AD, 4.5% [CI, –1.1% to 10%]]</td>
<td>10 vs 10</td>
<td>SPRING-2 [38, 39]</td>
</tr>
</tbody>
</table>

**Abbreviations:** AD, adjusted difference; AE, adverse event; CI, confidence interval (95%); DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; RAL, raltegravir; RTV, ritonavir.

^a Comparator group vs DTG.
^b Dose of DTG 10 mg daily.
^c Time to loss of virologic response analysis of patients with human immunodeficiency virus (HIV) RNA level <50 copies/mL through week 96 (comparator vs DTG).
^d Dose of DTG 25 mg daily.
^e Dose of DTG 50 mg daily.
^f HIV RNA level <50 copies/mL at week 48 (comparator vs DTG) via Food and Drug Administration (FDA) snapshot algorithm.
^g HIV RNA level <50 copies/mL at week 96 (comparator vs DTG) via FDA snapshot algorithm.

### Table 2. Major Clinical Trials of Dolutegravir in Antiretroviral-Experienced Participants

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Comparator</th>
<th>No. of Participants</th>
<th>Virologic Efficacy, %</th>
<th>No. Stopped Due to AE^a</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 INSTI naive</td>
<td>RAL</td>
<td>361</td>
<td>64 vs 71^b [AD, 7.4% [CI, 7.1%–14.2%]]</td>
<td>14 vs 9^c</td>
<td>SAILING [40]</td>
</tr>
<tr>
<td>2b RAL resistant</td>
<td>DTG</td>
<td>24^d cohort II 27^e cohort I</td>
<td>96 vs 78^d (P = .017)</td>
<td>0 vs 2^e</td>
<td>VIKING [41]</td>
</tr>
<tr>
<td>3 RAL or EVG resistant</td>
<td>None</td>
<td>NA</td>
<td>82^g 69^h</td>
<td>6</td>
<td>VIKING-3 [32, 33]</td>
</tr>
</tbody>
</table>

**Abbreviations:** AD, adjusted difference; AE, adverse event; CI, confidence interval (95%); DTG, dolutegravir; EVG, elvitegravir; INSTI, integrase strand transfer inhibitor; NA, not applicable; RAL, raltegravir.

^a DTG dosed at 50 mg daily.
^b Human immunodeficiency virus (HIV) RNA level <50 copies/mL at week 48 (comparator vs DTG) via Food and Drug Administration (FDA) snapshot algorithm.
^c Comparator group vs DTG.
^d DTG dosed at 50 mg twice a day.
^e Proportion of subjects on day 11 (after a 10-day functional monotherapy phase of DTG plus failing regimen) with HIV RNA level <400 copies/mL or ≥0.7 log_{10} copies/mL below the baseline value.
^f HIV RNA levels <50 copies/mL at week 24 via the FDA time to loss of virologic response algorithm.
^g Percentage of subjects on day 8 (after a 7-day functional monotherapy phase of DTG plus failing regimen) with HIV RNA of <50 copies/mL or >1 log_{10} decline from baseline.
^h Percentage of subjects with HIV RNA levels <50 copies/mL at week 24 via the FDA snapshot algorithm.
participants achieved the primary endpoint at day 11, whereas 96% did in cohort II. By week 24, 41% and 75% of participants in cohorts I and II, respectively, had VL <50 copies/mL via the time to loss of virologic response algorithm. Integrate resistance did develop in 15% of all participants and were classified as RAL mutations. No single mutation emerged that appeared to significantly decrease DTG susceptibility based on the current knowledge of DTG resistance pathways [41]. Finally, a larger, ongoing study (VIKING-3) in heavily treated participants with advanced disease and multidrug resistance, including RAL or EVG resistance, showed that 84% of participants given DTG 50 mg twice daily in addition to the OBR with either no primary INSTI mutations or an N155, Y143, or T66 mutation achieved HIV RNA load <50 copies/mL at week 24 with minimal toxicity [32] (Table 2).

ADVERSE EVENTS

Based on available clinical information to date, DTG has relatively few side effects and is well tolerated compared with most other available antiretrovirals, but postmarketing data is limited. The rate of adverse events leading to DTG discontinuation in most studies is 2%–3% [33,36,38,40]. Reactions of at least moderate intensity (grade 2–4) occurring in ≥2% of treatment-naive participants on DTG were insomnia (3%) and headache (2%) [36,38]. Hypersensitivity reactions have been reported, but in ≤1% [11]. As expected, based on the drug’s known inhibition of the renal organic cation transporter, OCT2, which causes a decrease in urinary creatinine secretion, DTG caused small mean elevations in serum creatinine in treatment-naive participants ranging from 0.1 to 0.2 mg/dL, which were typically evident by 2–4 weeks and remained stable until drug discontinuation [35–39,42]. These were not thought to represent true changes in the glomerular filtration rate (GFR), based on the findings of a phase 1 study in healthy adults that showed lack of GFR decrease as measured by iothalamate clearance when participants were given DTG 50 mg once or twice daily (vs placebo) [43].

CONCLUSIONS

Dolutegravir has proven to be clinically noninferior and, in some studies, superior to current first-line ART, including the 1 pill once a day coformulation containing TDF/FTC/EFV. It is well tolerated and is conveniently dosed once daily without boosting in ART-naive or ART-experienced, INSTI-naive patients. It has a higher barrier to resistance than other INSTIs. Although the drug has primarily been studied in men, it is expected to have similar responses in women with HIV infection. The Panel on Antiretroviral Guidelines for Adults and Adolescents issued a statement in October 2013 placing DTG in combination with TDF/FTC or ABC/3TC on the list of preferred regimens in ART-naive persons given its performance in clinical trials [44]. Of note, a coformulated pill combining DTG/ABC/3TC as a single once-daily regimen is under study [45]. Given its relatively minimal drug interaction and side-effect profile, DTG may prove useful for patients on other medications for tuberculosis, hepatitis C, seizure, or contraception as well as those intolerant to other ART. In addition, DTG appears to be a viable choice for salvage in some highly treatment-experienced patients harboring resistance to the first-generation INSTIs (RAL and EVG), provided that integrase genotypes indicate ongoing DTG susceptibility. However, continued patient exposure to RAL or EVG in the setting of virologic failure may lead to the accumulation of certain INSTI mutations that could decrease the likelihood of DTG susceptibility in the future. Dolutegravir is a welcome addition to the HIV treatment armamentarium and it appears that it will have wide applicability.

Note

Potential conflicts of interest. Both authors: No reported conflicts. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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