Dolutegravir: An Integrase Strand Transfer Inhibitor for the Treatment of Human Immunodeficiency Virus 1 in Adults

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Abstract

Objective: To review the efficacy, safety, pharmacokinetics, pharmacodynamics, administration, drug interactions, and cost of dolutegravir (Tivicay), a third in class integrase strand transfer inhibitor (INSTI), for the treatment of human immunodeficiency virus (HIV-1) in adults. **Data Sources:** MEDLINE, *International Pharmaceutical Abstracts*, ClinicalTrials.gov, and Google Scholar searches (January 2000 to May 2014) were conducted for articles published in English and limited to human subjects, using the key words antiretroviral drugs, HIV integrase strand transfer inhibitors, dolutegravir, DTG, and S/GSK1349572. **Study Selection and Data Extraction:** Following MEDLINE, *International Pharmaceutical Abstracts*, ClinicalTrials.gov, and Google Scholar searches, 6 clinical trials were identified and included in this review. Phase III/IV studies evaluating the safety and efficacy of dolutegravir in humans were selected and evaluated. **Data Synthesis:** In treatment naïve and experienced patients dolutegravir was noninferior to raltegravir at suppressing viral load when added to background therapy. Abacavir/lamivudine/dolutegravir was noninferior to efavirenz/emtricitabine/tenofovir disoproxil fumarate and darunavir/ritonavir plus background therapy at suppressing viral load. In patients with multiple-class antiretroviral resistance at baseline, dolutegravir decreased HIV RNA by 1.4 log₁₀ copies/mL at day 8, 63% of patients had achieved virologic suppression at week 8, and retained potency in treatment-experienced INSTI-resistant patients up to week 48 or 96 of follow-up. **Conclusion:** Dolutegravir is a safe, effective, and well-tolerated treatment option for adults with HIV-1, even in the setting of resistance to other antiretrovirals.

Keywords

antiretrovirals, HIV/AIDS, infectious disease, evidence-based medicine, drug trials

Introduction

Human immunodeficiency virus (HIV) is a blood-borne lente- and retrovirus that leads to the acquired immune deficiency syndrome (AIDS).¹ HIV affects 24 million people worldwide and 1.2 million people in the United States.^{2,3} HIV may present in 1 of 2 subtypes: HIV-1 or HIV-2. HIV-1 is the most common, more likely to advance to AIDS, and infects patients worldwide.⁴ HIV can additionally be subdivided into clinical classifications A, B, and C based on CD4⁺ cell counts and clinical presentation.^{5,6}

The HIV viral life cycle consists of adsorption of virus to host cell, entry into host cell, integration into host RNA, reverse transcription to DNA via reverse transcriptase, and integration into nucleus via integrase. Next, within the nucleus, proviral DNA is assembled and then transcribed to viral RNA. Viral RNA is then translated to protein, assembled, and buds off from the host cell. After budding the virion matures via protease and is then considered infectious.¹

Available medications to treat HIV act at many points in the viral life cycle, including the times of entry, reverse transcription, integration, and at time of maturation. Antiretroviral medications treat HIV infection, reduce morbidity, and decrease disease progression. These include coreceptor inhibitors, fusion inhibitors, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), and protease inhibitors.^{1,7-10} Efficacy of these medications is measured by the reduction in the HIV RNA (also known as “viral load”) and the

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increase in CD4⁺ cell count. Both measures should be obtained before initiating therapy and periodically throughout treatment.¹¹ According to current guidelines, initiation of antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of disease progression; however, each recommendation is based on varied levels of evidence.¹² The strongest level of evidence is initiation of ART in patients with CD4⁺ cell counts <350 cells/mm³.¹² Treatment should also be considered in patients with CD4⁺ cell counts 350 to 500 cells/mm³ and >500 cells/mm³.¹² According to guidelines and the AIDS Clinical Trials Group (ACTG), virologic failure is defined as HIV RNA level of >200 copies/mL.¹³

Dolutegravir (Tivicay) is a second-generation INSTI approved August 12, 2013, by the Food and Drug Administration to treat HIV in both treatment-naïve and treatment-experienced patients.¹⁴ ViiV Healthcare (Research Triangle Park, NC) holds the patent for dolutegravir, and GlaxoSmithKline manufactures the medicine in the same locale. Dolutegravir is the third in class integrase strand transfer inhibitor: raltegravir (Isentress) and elvitegravir (compounded as a combination product with cobicistat, emtricitabine, and tenofovir disoproxil fumarate; Stribild) are also available in the United States.^{15,16} All 3 INSTIs are recommended by National Institutes of Health guidelines as an option for initial treatment of naïve HIV infection.¹⁷ Here, we review the efficacy, safety, pharmacokinetics, pharmacodynamics, and clinical application of dolutegravir in the treatment of HIV-1 in adult patients.

Pharmacology

Dolutegravir inhibits the action of viral enzyme integrase by binding and antagonizing the integrase active site. This prevents HIV from incorporating its DNA into the DNA of the host cell, thus blocking the strand transfer step of retroviral DNA integration.⁷

In cell culture dolutegravir exhibits antiviral activity against laboratory strains of wild-type HIV-1 with mean half maximal effective concentration (EC_{50}) values of 0.5 nM to 2.1 nM in peripheral blood mononuclear cells (PBMCs) and membrane type (MT)-4 cells.⁷ Dolutegravir-resistant viruses were selected in cell culture, and up to a 4-fold decrease in susceptibility of HIV-1 to dolutegravir were seen with the single nucleotide polymorphisms (SNPs) E92Q, G118R, S153/Y, G193E, or R263K.⁷ Mutant viruses containing Q148R or Q148H substitutions conferred decreased susceptibility to dolutegravir by 13- and 46-fold decrease, respectively.⁷ Decreases in dolutegravir susceptibility have occurred in INSTI-resistant HIV-1. Among 60 mutant HIV-1 viruses, single INSTI-resistant substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in susceptibility. Combinations of multiple INSTI-resistant SNPs such as T66K/L74M, E92Q/N155H, G140C/

Q148R, G140S/Q148H, R, or K, Q148R/N155H, T97A/G140S/Q148, and E138/G140/Q148 also conferred a greater than 2-fold decrease in dolutegravir susceptibility.⁷ Dolutegravir has less resistance overlap with raltegravir than does elvitegravir. This allows dolutegravir to possibly retain activity against strains containing Y143 and N155 mutations, which confer resistance to raltegravir with possible cross-resistance to elvitegravir.^{18,19}

When tested in combination with other antiviral agents, the antiviral activity of dolutegravir was not antagonistic when combined with efavirenz, nevirapine, abacavir sulfate, maraviroc, enfuvirtide, adefovir dipivoxil, or ribavirin.⁷

Pharmacokinetics and Pharmacodynamics

The pharmacokinetic properties of dolutegravir have been evaluated in both healthy adults and HIV-1-infected adults, and exposure to drug was generally similar in both populations.⁷ Dolutegravir is administered as an oral tablet with no need for pharmacokinetic boosting unlike elvitegravir.²⁰⁻²² Dolutegravir may be taken without regard to food, which allows for convenient dosing. A phase IIB clinical trial (SPRING-1) showed subjects who received dolutegravir with or without food tolerated the drug well.^{22,23} Another study has shown that ingesting low-fat (300 kcal, 7% fat), moderate-fat (600 kcal, 30% fat), and high-fat (870 kcal, 53% fat) meals increased dolutegravir $AUC_{(0-\infty)}$ by 33%, 41%, and 66%, respectively. Low-fat, moderate-fat, and high-fat meals also increased C_{max} by 46%, 52%, and 67%, respectively, and prolonged T_{max} from 2 hours under fasted conditions to 3, 4, and 5 hours, respectively.^{7,23} Although food slowed the rate of absorption, and increased the extent of absorption, the effect is not considered clinically important.^{7,22,23} Following oral administration peak plasma concentrations were observed 2 to 3 hours postdose, with steady state achieved within 5 days after initiation of once-daily dosing. Above a 50 mg dose, dolutegravir plasma concentrations increased in a nonlinear manner; therefore, 50 mg once- or twice-daily dosing was established instead of 100 mg once daily.^{7,21}

Dolutegravir is highly protein bound to human plasma proteins at $\geq 98.9\%$, and binding is independent of plasma concentration. The apparent volume of distribution (V_d/F) following administration is estimated at approximately 17.4 L, though the absolute bioavailability (F) of dolutegravir has not been established.⁷

Dolutegravir metabolism occurs primarily by the liver via uridine diphosphate glucuronosyltransferase (UGT) 1A1 with some contribution from CYP450 3A4.²⁴ Dolutegravir is an in vitro substrate for P-glycoprotein, breast cancer resistance protein, UGT1A3, and UGT1A9, and also inhibits the renal organic cation transporter 2 (OCT2). After a single dose of dolutegravir, 53% was excreted unchanged in feces

and 31% was excreted via urine as various by-products. Urine by-products identified include an inactive ether glucuronide (18.9% of total dose) formed by UGT1A1, an oxidized benzylic carbon metabolite (3% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose).^{7,24} Renal elimination of unchanged drug is less than 1%. Dolutegravir has a terminal half-life of approximately 14 hours, and an apparent clearance (CL/F) of 1 L/h based on population kinetics among individuals with HIV-1.⁷

Clinical Efficacy

Four clinical trials, SPRING-2, SINGLE, SAILING, and VIKING-3, led to the approval of dolutegravir. Two additional trials, FLAMINGO and VIKING-4, are also underway. Throughout most trials, clinical efficacy of dolutegravir was defined as virologic suppression of HIV-1 RNA <50 copies/mL. All studies are summarized in Table 1.

Treatment-Naïve Patients

The efficacy of dolutegravir in treatment-naïve HIV-1 infected adults is based on the data from 2 phase III clinical trials, SPRING-2 and SINGLE.

SPRING-2 is an ongoing 96-week, phase III, randomized, double-blind, double-dummy, active-controlled, international, multicenter, noninferiority study (–10% noninferiority criterion).²⁵ A total of 822 treatment-naïve subjects were randomized to receive either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily. Both groups were also given either abacavir sulfate/lamivudine or emtricitabine/tenofovir disoproxil fumarate as background regimen. The primary end point was the percentage of participants with virologic suppression at week 48.²⁵ Patients were 13% female, 15% non-white, 11% had hepatitis B and/or C virus co-infection, 2% CDC Class C, 28% HIV-1 RNA >100 000 copies/mL, 48% CD4+ cell count <350 cells/mm³, and 39% received abacavir sulfate/lamivudine.^{7,25}

A total of 808 subjects were included in the efficacy and safety analyses.⁷ At 48 weeks, 88% of patients in the dolutegravir group achieved the primary endpoint compared with 86% in the raltegravir group. The absolute difference was adjusted for baseline HIV-1 RNA and investigator selected backbone dual NRTI therapy to give an adjusted treatment difference of 2.5%; 95% confidence interval (CI) = –2.2 to 7.1, $P = \text{NS}$.^{7,25} The authors concluded that dolutegravir was noninferior to raltegravir.²⁵ Virologic outcomes were comparable across baseline characteristics including CD4+ cell count, age, and use of the background regimens.²⁵ The median increase in CD4+ cell counts from baseline for both groups was 230 cells/mm³ at 48 weeks. No treatment-emergent resistance in patients on dolutegravir were observed, one was seen with raltegravir, and 4 NRTI treatment-emergent

resistances were noted.²⁵ The most common adverse drug events (ADEs) in the dolutegravir versus raltegravir were nausea (14% vs 13%, respectively), diarrhea (11% in both groups), headache (12% in both groups), and nasopharyngitis (11% vs 12%, respectively), and none were significantly different. The tolerability of each drug was similar with approximately 2% of patients discontinuing due to an ADE, and ≤1% experiencing serious ADEs.^{7,25,31} Serum creatinine increased 12.3 mmol/L in the dolutegravir group and 4.7 mmol/L in the raltegravir group.³²

At 96 weeks, 827 subjects were analyzed. The results showed dolutegravir remains noninferior to raltegravir and has a sustained response through 96 weeks with an adjusted treatment difference of 4.5%; 95% CI = –1.1 to 10.0, $P = \text{NS}$.³² At 96 weeks, 81% of patients in the dolutegravir group achieved virological suppression compared with 76% in the raltegravir group.³² The median increase in CD4+ cell count was similar through week 96 with 276 cells/mm³ for dolutegravir and 264 cells/mm³ for raltegravir. ADEs remained consistent among dolutegravir versus raltegravir: nausea (15% vs 14%, respectively), diarrhea (14% vs 13%, respectively), headache (14% vs 13%, respectively), and nasopharyngitis (13% vs 14%, respectively). Although discontinuation due to ADEs was 2% in both groups from week 48, only 3 raltegravir subjects experienced events leading to withdrawal and no subjects in the dolutegravir arm withdrew. At the end of 96 weeks a low rate of protocol-defined virologic failure (HIV-1 RNA ≥ 50 copies/mL at week 24) was seen in the dolutegravir arm (5% vs 7%) and no resistance mutations were observed. No further increase in serum creatinine was observed between 48 and 96 weeks.³²

SINGLE was a 96-week, phase III, randomized, double-blind, double-dummy, active-controlled, international, multicenter, noninferiority study (–10% noninferiority criterion). A total of 833 treatment-naïve subjects were randomized to receive dolutegravir 50 mg once daily plus abacavir sulfate/lamivudine, or efavirenz/emtricitabine/tenofovir disoproxil fumarate. Virologic suppression was the primary endpoint at 48 weeks. The proportion of subjects with virologic suppression in the dolutegravir group versus the efavirenz/emtricitabine/tenofovir disoproxil fumarate group was 88% and 81%, respectively (treatment difference 7.4%, 95% CI = 2.5% to 12.3%, $P = .003$).²⁶ Patients were 16% female, 32% non-white, 7% had hepatitis C co-infection (hepatitis B virus co-infection was excluded), 4% CDC Class C, 32% HIV-1 RNA >100 000 copies/mL, and 53% CD4+ cell count <350 cells/mm³.^{7,26} The median increase in CD4+ cell counts from baseline for dolutegravir and efavirenz/emtricitabine/tenofovir disoproxil fumarate was 267 cells/mm³ and 208 cells/mm³, respectively ($P < .001$).²⁶ No treatment-emergent resistance was seen in the dolutegravir arm; however, in patients who received efavirenz/emtricitabine/tenofovir disoproxil fumarate, 1 treatment-emergent resistance was

Table I. Summary of Clinical Trials of Dolutegravir.

Trial	Phase	Design	Dose(s)	Primary Endpoint	Primary Endpoint Results
SPRING-2 ²⁵ ; Treatment naïve	III	R, DB, DD, AC, MC, NI	Dolutegravir 50 mg daily + BGT or raltegravir 400 mg BID + BGT BGT: either abacavir sulfate/lamivudine or tenofovir disoproxil fumarate/emtricitabine	Percentage of participants with HIV-1 RNA below 50 copies/mL at 48 weeks	Dolutegravir: 88% Raltegravir: 86% CD4+ cell count increase: 230 cells/mm ³ in each arm
SINGLE ²⁶ ; Treatment naïve	III	R, DB, DD, AC, MC, NI	Dolutegravir 50 mg daily + abacavir sulfate/lamivudine daily or efavirenz/emtricitabine/tenofovir disoproxil fumarate daily	Percentage of participants with HIV-1 RNA below 50 copies/mL at 48 weeks	Dolutegravir: 88% Efavirenz/emtricitabine/tenofovir disoproxil fumarate: 81% (<i>P</i> = .003) CD4+ cell count increase: Dolutegravir: 267 cells/mm ³ Efavirenz/emtricitabine/tenofovir disoproxil fumarate: 208 cells/mm ³ (<i>P</i> < .001)
SAILING ²⁷ ; Treatment experienced; INSTI naïve	III	R, DB, AC, MC, PG, NI	Dolutegravir 50 mg daily + BGT or raltegravir 400 mg BID + BGT	Percentage of participants with HIV-1 RNA <50 copies/mL at 48 weeks	Dolutegravir: 71% Raltegravir: 64% <i>P</i> = .03 CD4+ cell count increase: Dolutegravir: 162 cells/mm ³ Raltegravir: 153 cells/mm ³
VIKING-3 ²⁸ ; Treatment experienced; INSTI experienced	III	OL, MC, Single arm	BGT of at least once fully active agent + no more than one second single agent which may or may not be active Dolutegravir 50 mg BID with current failing regimen for 7 days; then OBR from day 8 Must have documented genotypic and/or phenotypic resistance to at least one compound in 2 or more of the other approved classes of ART but must also be able to include at least one fully active drug in the OBR to be started day 8	1. Number of participants with AE of the indicated severity, per the DAIDS grading scale 2. Number of participants with HIV-1 RNA <50 copies/mL at week 24 3. Mean change from baseline in plasma HIV-1 RNA at day 8 4. Number of participants with the maximum post-baseline-emergent clinical chemistry toxicities of the indicated grade	At 24 weeks: dolutegravir 63%

(continued)

Table 1. (continued)

Trial	Phase	Design	Dose(s)	Primary Endpoint	Primary Endpoint Results
VIKING-4 ²⁹	III	R, DB, MC, PC (7 days)	Dolutegravir 50 mg BID or placebo with current failing regimen for 7 days	5. Number of participants with any AE or SAE	At day 8: Dolutegravir: $-1.06 \log_{10}$ copies/mL
		OL (from day 8)	At day 8: dolutegravir 50 mg BID + BGT	6. Number of participants with the maximum post-baseline-emergent hematology toxicities of the indicated grade Mean change from baseline in HIV-1 RNA <50 copies/mL to day 8	
FLAMINGO ³⁰	IIIb/IV	R, OL, AC, PG, MC, NI	BGT of at least once fully active agent Dolutegravir 50 mg daily + BGT or darunavir 800 mg/ritonavir 100 mg daily + BGT	Percentage of participants with HIV-1 RNA <50 copies/mL at 48 weeks	Placebo: $+0.10 \log_{10}$ copies/mL $P \leq .001$ Dolutegravir: 90%
			BGT: either abacavir sulfate/lamivudine or tenofovir disoproxil fumarate/emtricitabine		
					Darunavir: 83%

Abbreviations: R, randomized; OL, open label; PG, parallel group; PB, partially blinded; DB, double blind; PC, placebo controlled; DD, double dummy; C, crossover; AC, active controlled; AUC, area under the curve; NI, noninferiority; BGT, background therapy; OBR, optimized background regimen; BID, twice daily; AE, adverse event; SAE, serious adverse event; DAIDS, Division of Acquired Immune Deficiency Syndrome.

observed to NRTIs and 4 to NNRTIs.²⁶ Eighty-nine percent of patients in the dolutegravir arm had an ADE compared to 82% in the efavirenz/emtricitabine/tenofovir disoproxil fumarate group. Nervous system ADEs were more common in the efavirenz/emtricitabine/tenofovir disoproxil fumarate group compared to the dolutegravir group (47% vs 22%, $P < .001$).²⁶ Statistically different nervous system ADEs included dizziness (more common in efavirenz/emtricitabine/tenofovir disoproxil fumarate arm, $P < .001$), abnormal dreams (more common in efavirenz/emtricitabine/tenofovir disoproxil fumarate arm, $P < .001$), and insomnia (more common in dolutegravir arm, $P = .029$).²⁶ Common nonnervous system ADEs were diarrhea (17% vs 18%, respectively), nasopharyngitis (15% vs 14%), and headache (13% for each).²⁶ Two percent of subjects in the dolutegravir group discontinued the study due to ADEs versus 10% in the efavirenz/emtricitabine/tenofovir disoproxil fumarate group (P value not reported [NR]).^{7,26,31} Noninferiority will also be assessed at week 96.⁷

Treatment-Experienced, INSTI-Naïve Patients

SAILING is an ongoing 48-week, phase III, randomized, double-blind, active-controlled, parallel-group, international, multicenter, noninferiority study (-12% non-inferiority criterion). A total of 719 HIV-1 infected, ART-experienced adult patients with at least 2-class drug resistance were randomized to receive either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily both with investigator-optimized background regimen. The background regimen consisted of up to 2 agents, one of which was fully active (defined as a drug that is likely to have antiretroviral activity based on the patient's treatment history and drug-resistance testing, or a novel mechanism of action).²⁷ The most common background regimens included darunavir/ritonavir/tenofovir disoproxil fumarate, lopinavir/ritonavir/tenofovir disoproxil fumarate, darunavir/ritonavir/etravirine, lopinavir/ritonavir, atazanavir/ritonavir/tenofovir disoproxil fumarate, and darunavir/ritonavir/maraviroc.²⁷ A total of 719 patients were recruited, and they were 32% female, 49% non-white, 16% hepatitis B and/or C virus co-infection, 46% CDC Class C, 20% HIV-1 RNA $>100\,000$ copies/mL, and 72% CD4+ cell count <350 cells/mm³.³ Baseline characteristics were similar between treatment groups. At week 48, 251 (71%) patients on dolutegravir had virologic suppression versus 230 (64%) patients on raltegravir. Absolute treatment differences were adjusted based on undefined baseline values to give an adjusted treatment difference of 7.4% (95% CI = 0.7% to 14.2%, $P = .03$).²⁷ Researchers concluded dolutegravir was noninferior to raltegravir. Per-protocol statistical superiority of dolutegravir versus raltegravir was established per a sequential testing procedure ($P = .03$, based on a 5% significance level).²⁷

The median increase in CD4+ cell counts from baseline for the dolutegravir group was 162 cells/mm³ and 153 cells/mm³

in the raltegravir group (P value NR).²⁷ Virologic failure occurred more frequently in the raltegravir group than in the dolutegravir group (12% vs 6%, respectively, P value NR). This may indicate a greater antiviral potency of dolutegravir in treatment-experienced, INSTI-naïve patients.²⁷ Treatment-emergent genotypic or phenotypic INSTI resistance occurred in 4 dolutegravir subjects versus 17 raltegravir subjects (adjusted difference -3.7% , 95% CI = -6.1 to -1.2 ; $P = .03$).²⁷ None of the subjects had detectable phenotypic decreases in susceptibility to either dolutegravir or raltegravir.^{7,31} The most common ADEs reported were diarrhea, upper respiratory tract infection, and headache. Three percent and 4% of patients in the dolutegravir and raltegravir groups, respectively, had an ADE leading to withdrawal of medication.^{7,27}

Treatment-Experienced, INSTI-Experienced Patients

VIKING-3 is an ongoing, phase III, open-label, single-arm multicenter trial. This study was designed to examine the antiviral activity and safety of dolutegravir-containing regimens in HIV-1 infected, ART and INSTI-experienced subjects with evidence of resistance to another INSTI. Enrolled subjects must have had documented genotypic and/or phenotypic resistance to at least one medication in 2 or more of the other approved classes of ART, and must be able to switch to one fully active drug in the optimized background regimen (OBR) as determined by a Monogram Biosciences Net Assessment (San Francisco, CA) during the trial.²⁸ The OBRs were diverse. The most commonly used agents, coadministered with dolutegravir 50 mg twice daily, were darunavir/ritonavir (65%), emtricitabine/tenofovir disoproxil fumarate (60%), etravirine (37%), enfuvirtide (32%), and maraviroc (25%).²⁸ The most frequently used active ARTs in OBR were tenofovir disoproxil fumarate (46%), enfuvirtide (28%), darunavir/ritonavir (25%), etravirine (22%), and maraviroc (18%).²⁸

Of the 183 enrolled subjects, 133 subjects had INSTI resistance at screening, and 50 subjects had only historical evidence of resistance.^{7,28} Subjects showed multiple-class ART resistance at baseline: 79% had at least 2 NRTIs, 75% had at least 1 NNRTI, and 71% had at least 2 protease inhibitor major substitutions; 62% had non-CCR5 HIV detected.⁷ Baseline characteristics included 23% female, 29% non-white, and 20% hepatitis B and/or C virus co-infection.^{7,28} Subjects received dolutegravir 50 mg twice daily with the current failing background regimen for 7 days, then dolutegravir 50 mg with OBR starting from day 8.⁷ At baseline median CD4+ cell count was 140 cells/mm³, median duration of prior ART was 13 years, baseline plasma HIV-1 RNA was 4.38 log₁₀ copies/mL, and 56% were CDC Class C.⁷ Primary endpoints were mean change from baseline in HIV-1 RNA at day 8 and number of participants with virologic suppression at week 24.²⁸

Mean HIV-1 RNA levels decreased by $1.4 \log_{10}$ copies/mL at day 8 (95% CI = $1.3 \log_{10}$ to $1.5 \log_{10}$, $P < .001$).²⁸ At week 24, 63% of patients had achieved virologic suppression.^{7,31} Certain INSTI-associated resistance substitutions present at baseline affected virologic outcomes at week 24. Only 18% of patients with the Q148H/R SNP plus 2 or more INSTI-resistance substitutions (ie, L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R) achieved virologic suppression.⁷ Eighty percent and 56% of patients with N155H or Y143C/H/R SNP without a Q148 substitution achieved virologic suppression, respectively.⁷ The rate of ADEs leading to discontinuation was low at 3%.^{7,28,31} The most common ADEs reported were diarrhea, nausea, and headache in only 5% of subjects.²⁸

Newer Trials in Progress

FLAMINGO is an ongoing 96-week phase IIIb/IV randomized, open-label, active controlled, parallel group, multicenter, noninferiority study (-12% criterion). FLAMINGO compares dolutegravir or darunavir/ritonavir in combination with dual NRTIs in treatment-naïve HIV-1-infected adults. Fixed-dose NRTIs include either abacavir sulfate/lamivudine or tenofovir disoproxil fumarate/emtricitabine. The primary endpoint was virologic suppression at 48 and 96 weeks.^{30,33,34}

At 48 weeks noninferiority of dolutegravir was demonstrated, and a prespecified superiority test was conducted.³³ Data showed 90% of dolutegravir subjects had virologic suppression compared with 83% in the darunavir group (adjusted treatment difference 7.1%; 95% CI = 0.9% to 13.2%, $P = .025$).³³

The most common ADEs in the dolutegravir and darunavir groups were diarrhea (17% and 29%, respectively), nausea (16% and 18%, respectively), and headache (15% and 10%, respectively, P values NR). Treatment withdrawal due to ADEs was 2% in the dolutegravir arm versus 4% in the darunavir arm. Dolutegravir subjects had few Grade 2 or higher abnormalities in fasting low-density lipoprotein cholesterol compared to darunavir (2% vs 7%, respectively, $P < .001$). No treatment-emergent viral mutations were seen.^{33,34}

VIKING-4 is an ongoing phase III, randomized, multicenter study that assesses dolutegravir efficacy and safety in treatment-experienced patients with HIV-1 and viral resistance to raltegravir and/or elvitegravir. In the double-blind phase, subjects were randomized to dolutegravir 50 mg twice daily versus placebo for 7 days. All subjects were coadministered current failing background regimen.²⁹ At day 8, in the open-label phase, all subjects, including those previously on placebo, received dolutegravir 50 mg twice daily with an optimized background regimen that contained at least one fully active drug. Primary endpoints included mean change from baseline in plasma HIV-1 RNA at day 8 adjusted

for baseline dolutegravir phenotypic fold change, activity of the failing background regimen, and baseline plasma HIV-1 RNA.²⁹

Results showed that treatment over 8 days with dolutegravir was superior to placebo in treatment-experienced INSTI-resistant patients. By week 8, a median CD4+ cell count increase of 32 cells/mm³ was observed in the dolutegravir arm from baseline, and 83 cells/mm³ in patients who were switched from placebo to dolutegravir. Fifty percent of subjects in the dolutegravir arm reported any ADE versus 13% in the placebo arm up to day 8. At week 8, 71% of patients in the dolutegravir arm and 50% of patients who were switched from placebo to dolutegravir reported an ADE, with headache (21% vs 6%, respectively), nausea (21% vs 6%), and diarrhea (14% vs 13%, respectively) as the most commonly reported ADEs.²⁹

Adverse Effects

Overall, dolutegravir appears to be generally well tolerated. Although changes in serum creatinine due to inhibition of tubular secretion have been seen, renal glomerular function was not affected.⁷ The most commonly observed ADEs in patients receiving once-daily dolutegravir were nausea, diarrhea, dizziness, nasopharyngitis, and headache, with most events being reported as being of either mild or moderate intensity.²⁵ With twice-daily dosing regimens, the most commonly reported ADEs were diarrhea, nausea, and headache.^{7,35} No significant abnormalities in lipid/liver chemistries were observed in healthy adults.^{7,22,35} Study discontinuation due to an adverse effect was typically low to uncommon with patients in the dolutegravir-treated group.^{21,22,25,27,36}

Drug Interactions

Dolutegravir is metabolized primarily through the UGT1A1, and less significantly by CYP450 3A4.²⁴ At therapeutic doses, dolutegravir is not an inhibitor of CYP or UGT enzymes.²⁴ Due to this mechanism of metabolism, drug-drug interactions with dolutegravir are limited. Several studies have investigated the potential drug interactions between dolutegravir and other ART as well as with other drugs. In vivo studies show that dosage adjustments for dolutegravir are not required when used in combination with treatments containing atazanavir sulfate, ritonavir, darunavir ethanolate, lopinavir, fosamprenavir calcium, entecavir, or tenofovir disoproxil fumarate. Nevirapine has been shown to decrease dolutegravir levels as a result of enzyme induction, and should not be coadministered with dolutegravir.³⁷⁻⁴⁰ Etravirine alone may significantly diminish levels of dolutegravir, and this combination should be avoided. However, dolutegravir may be coadministered with etravirine if given with ritonavir-boosted protease

inhibitors.⁴¹ When used in combination with other ART, consideration should be given to interactions relevant to other components of the therapeutic regimen.

Dolutegravir should not be used in combination with dofetilide because dolutegravir inhibits OCT2, which is responsible for the active secretion of dofetilide into the renal tubule. Combinations of dofetilide and dolutegravir may increase dofetilide levels and patients' risk for serious and life-threatening arrhythmias.⁷ Inhibition of OCT2 also may lead to increases in plasma metformin levels, and patients taking metformin should be closely monitored when starting or stopping dolutegravir. Dose adjustment of metformin may be necessary.⁷ Multivitamins, proton pump inhibitors, and H2 antagonists may all be used in conjunction with dolutegravir without significant impact on drug concentrations.⁴² Similarly, no dose adjustment is needed when coadministering dolutegravir with either prednisone or methadone.^{43,44} Iron supplements or antacid products containing divalent cations such as aluminum and magnesium should be administered either 2 hours before or 4 hours following a dose of dolutegravir.⁴²

Precautions and Contraindications

Due to the potential risk of life-threatening arrhythmias, coadministration of dolutegravir with dofetilide is contraindicated.⁷ Dolutegravir should be avoided in patients with prior hypersensitivity to dolutegravir. Although subjects with hepatitis B and/or C virus co-infection were permitted to enroll in clinical studies, caution should be taken as they may be at increased risk for transaminase elevations with use of dolutegravir. As a result, liver enzymes should be monitored in patients with hepatic disease prior to initiating and during dolutegravir therapy. Those receiving combination ART with dolutegravir may develop immune reconstitution syndrome, an inflammatory response to indolent or residual opportunistic infections or autoimmune disorders. Syndrome onset is variable occurring from the initial phase to many months after initiation of dolutegravir therapy.⁷ Dolutegravir is rated as a pregnancy category B since animal studies have failed to demonstrate a risk to the fetus. There are no adequate studies in pregnant women thus far, and an Antiretroviral Pregnancy Registry has been established per the manufacturer.^{7,31} Due to the potential of HIV transmission, mothers should be instructed not to breastfeed while taking dolutegravir.⁷ Caution should be exercised in those aged 65 years and older due to insufficient representation in clinical trials.

Special Populations

Hepatic Impairment

In a small study ($n = 16$), adult patients with moderate hepatic impairment (Child-Pugh B) were compared to healthy controls and exhibited no clinically significant pharmacokinetic

differences.⁴⁵ No dose adjustment is needed for patients with mild to moderate hepatic impairment (Child-Pugh A or B).⁷ Data are currently unavailable for patients with severe hepatic impairment (Child-Pugh C); therefore, dolutegravir is not recommended in those patients. Patients with hepatitis B or C should have transaminases monitored at baseline and throughout treatment with dolutegravir.^{7,45}

Renal Impairment

The effect of dolutegravir on renal function was first evaluated in a phase 1 clinical study that assessed the renal function via measurement of iothexol and para-aminohippurate clearance in healthy adult subjects.⁴⁶ Healthy patients received dolutegravir 50 mg once daily, dolutegravir 50 mg twice daily, or placebo once daily for 14 days. Creatinine clearance decreased in both once-daily and twice-daily dosing by 9% and 13%, respectively, likely due to the inhibition of tubular secretion of creatinine. This study established that neither once- nor twice-daily dosing of dolutegravir had a significant effect on the actual glomerular filtration rate or effective renal plasma flow compared with the placebo.⁴⁶

Eight adult patients with severe renal impairment (CrCL <30 mL/min, not on dialysis) were compared to 8 healthy controls.⁴⁷ Patients with severe renal impairment exhibited decreased AUC, C_{max} , and C_{24h} by 40%, 23%, and 43%, respectively. The cause of the decrease in drug exposure is unknown.^{7,47} However, since there was less than the 75% reduction in dolutegravir exposure between the 50 mg and 10 mg once-daily doses observed in SPRING-1, the moderate effect of severe renal impairment is not considered clinically significant.⁴⁷ Population analysis from phase III studies, SAILING and VIKING-3, indicated that mild and moderate renal impairment had no clinically significant effect on the exposure to dolutegravir since subjects showed equivalent virologic response despite lower exposure.⁴⁷ No dosage adjustment is necessary for treatment-naïve, treatment-experienced, INSTI-naïve, or some INSTI-experienced patients with renal impairment. In patients with severe renal impairment and raltegravir-resistant HIV, caution should be used since the decrease in dolutegravir exposure may result in loss of therapeutic effect and development of resistance. Dolutegravir has not been studied in patients requiring dialysis.^{7,46,47}

Polymorphism in Drug-Metabolizing Enzymes

Patients with genetic polymorphisms in the UGT1A1 enzyme may also require special consideration, as poor, rapid, and loss of function alleles may lead to changes in dolutegravir concentration. In healthy adult subjects, individuals with UGT1A1 genotypes that confer poor metabolism had a 32% lower clearance and 46% higher AUC than individuals with UGT1A1 genotypes that confer normal metabolism.⁷

Cost Considerations

The average wholesale acquisition cost of dolutegravir is \$1175.40 per package of 30 tablets, which provides a 1-month supply.⁴⁸ Alternatively, the cost of a 1-month supply of raltegravir varies and the 25 mg, 100 mg, and 400 mg tablets are \$67.14, \$268.54, and \$1074.08, respectively.⁴⁹ The third agent in the INSTI class, elvitegravir, available only as a combination product with cobicistat/emtricitabine/tenofovir disoproxil fumarate, costs \$2342.47 for a 1-month supply.⁵⁰ While the cost is double that of dolutegravir, it also supplies 3 other medications in the combination pill and as a single dose. Consideration to the patient's out-of-pocket cost should be given when selecting treatment.

Dosage and Administration

Dolutegravir is supplied as yellow, round, film-coated, biconvex oral tablet available in 50 mg strength. The recommended daily dose of dolutegravir is dependent on various patient characteristics including coadministered medications. Treatment-naïve or treatment-experienced INSTI-naïve patients should take 50 mg once daily. Treatment-naïve or treatment-experienced INSTI-naïve patients, when coadministered with potent UGT1A/CYP3A inducers (ie, efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, rifampin), should take 50 mg twice daily. INSTI-experienced with INSTI-resistance or associated resistance substitutions also require 50 mg twice-daily dosing.⁷ No renal dose adjustments are necessary. Caution should be used in those with an estimated creatinine clearance <30 mL/min who are INSTI-experienced and have certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance as dolutegravir concentrations may be reduced resulting in loss of therapeutic effect and increased risk of resistance.⁷ Dolutegravir has not been studied in those with end-stage renal disease. No dosage adjustments are necessary for patients with mild to moderate hepatic disease (Child-Pugh Score A or B).⁷ Dolutegravir should be avoided in those with those with severe hepatic impairment (Child-Pugh Score C) since studies are lacking.⁷ While food has demonstrated a modest increase dolutegravir concentration, the effect has not been considered clinically significant, and dolutegravir may be taken with or without food.⁷ Dolutegravir should be taken 2 hours before or 6 hours after taking medications containing polyvalent cations such as antacids or certain laxatives.⁷ Tablets should be stored at room temperature (25°C), with an acceptable range of 15°C to 30°C.⁷

Patient Counseling

Patients taking dolutegravir should be counseled on the risk for hypersensitivity reaction, which may have many manifestations. Instruct patients to stop taking dolutegravir if they develop a rash, oral blisters, general malaise, muscle

weakness, facial swelling, fever, or any symptoms of liver failure (jaundice, change in urine color, tender upper right quadrant pain, etc). Patients should not take dolutegravir if also taking dofetilide. Patients taking metformin should be closely monitored. Treatment with dolutegravir will require monitoring of liver functions test in patients with hepatitis B and C. Fat redistribution may occur, and long-term cardiovascular effects of redistribution are unknown. Some patients with advanced HIV disease may develop an inflammatory response to the initiation of dolutegravir known as immune reconstitution inflammatory syndrome (IRIS). Patients should immediately inform their primary care provider if any symptoms of infection occur, as it may be a symptom of IRIS. Patient education regarding use of condoms to prevent transmission of HIV infection should also be provided. If a dose is missed, it should be taken as soon as it is remembered. If the next dose is due within the next 4 hours, the patient should skip the missed dose to avoid doubling up on medication.⁷

Potential Role in Therapy and Conclusions

Dolutegravir has been shown to be noninferior to raltegravir. Current trials have not demonstrated superiority over raltegravir, with the exception of the SAILING study, where dolutegravir showed a greater antiviral potency in treatment-experienced, INSTI-naïve patients and a lower rate of INSTI resistance. In treatment-experienced, INSTI-experienced patients, dolutegravir may have a role in therapy for patients who have shown resistance to another INSTI-containing regimen.

Advantages of dolutegravir include convenient once-daily dosing in many patients, versus twice-daily dosing of raltegravir. This may favor its use in postexposure prophylaxis with once-daily tenofovir disoproxil fumarate/emtricitabine. However, twice-daily dosing is recommended in the presence of potent UGT1A/CYP3A inducers or those patients suspected to have INSTI-resistant mutations. Unlike elvitegravir, dolutegravir does not need to be boosted. Due to the method of metabolism, drug interactions with dolutegravir are limited, and it can be taken without regard to meals. However, dolutegravir should not be coadministered with dofetilide, and caution should be exercised when used with metformin, iron supplements, antacids, and saline laxatives.

Overall, dolutegravir is well tolerated and disadvantages to the use of dolutegravir are few. Results from the ongoing studies will offer better insight into the role of dolutegravir in the treatment of both treatment-naïve and treatment-experienced HIV-1 infected adults. While currently reported data have been encouraging and demonstrated potential roles and benefits of the use of dolutegravir in therapy, additional long-term data will be necessary to firmly establish it as a therapy to take precedence over raltegravir in the treatment of HIV-1.

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