

HIGHLIGHTS OF PRESCRIBING INFORMATION

PDM | Schedule: S2 | N3S | PP

These highlights do not include all the information needed to use DOLUTEGRAVIR TABLETS safely and effectively. See full prescribing information for DOLUTEGRAVIR TABLETS.

DOLUTEGRAVIR TABLETS, for oral use
Initial U.S. Approval: 2013

INDICATIONS AND USAGE
Dolutegravir tablets are an HIV-1 integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults (treatment-naïve or experienced) and in pediatric patients (treatment-naïve or experienced) and weighing at least 14 kg (1).
Dolutegravir tablets are indicated in combination with rilpivirine as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who have virologically suppressed HIV-1 RNA less than 50 copies per mL on a stable antiretroviral regimen for at least 6 months with no history of treatment failure or known substitutions associated with resistance to either antiretroviral agent (1).

DOSE AND ADMINISTRATION
• Pregnancy Testing: Pregnancy testing is recommended before initiation of dolutegravir tablets in adolescents and adults of childbearing potential (2.1, 5.3, 8.1, 8.3).
• May be taken without regard to food (2.2, 2.6).

Population	Dose
Treatment-naïve or treatment-experienced INSTI-naïve or virologically suppressed (HIV-1 RNA <50 copies per mL) adults switching to dolutegravir plus rilpivirine (2.2)	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A1 or CYP3A inducers (2.2, 7.2, 7.3)	50 mg once daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance (2.2, 12.4)	50 mg once daily

*Rilpivirine dose is 25 mg once daily for those switching to dolutegravir plus rilpivirine.
*Alternative combinations that do not include metabolic inducers should be considered where possible.

Pediatric Patients: Treatment-naïve or treatment-experienced INSTI-naïve patients weighing at least 14 kg. See Table 4 for complete pediatric dosing recommendations (2.5). Dolutegravir tablets and dolutegravir tablets for oral suspension are not bioequivalent at the same dose (see **Pharmacokinetics** (12.3)).
If certain UGT1A1 or CYP3A inducers are coadministered, then adjust the weight-based dose of dolutegravir tablets to twice daily (5.2, 7.2, 7.3).
Dosing recommendations for dolutegravir tablets for patients weighing at least 14 kg (Table 4):
• 14 kg to less than 20 kg: 40 mg once daily.
• 20 kg and greater: 50 mg once daily.

DOSE FORMS AND STRENGTHS

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1 INDICATIONS AND USAGE
Dolutegravir tablets are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults (treatment-naïve or experienced) and in pediatric patients (treatment-naïve or experienced) but integrase strand transfer inhibitor (INSTI-naïve) weighing at least 14 kg (see **Microbiology** (12-4)).

Dolutegravir tablets are indicated in combination with rilpivirine as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who have virologically suppressed HIV-1 RNA less than 50 copies per mL on a stable antiretroviral regimen for at least 6 months with no history of treatment failure or known substitutions associated with resistance to either antiretroviral agent.

2 DOSE AND ADMINISTRATION

2.1 Pregnancy Testing before Initiation
Pregnancy is recommended testing before initiation of dolutegravir tablets in adolescents and adults of childbearing potential (see **Warnings and Precautions** (5.3)). Use in *Specific Populations* (8.1, 8.3).

2.2 Recommended Dose in Adults
Dolutegravir tablets may be taken with or without food.

Table 1. Dosing Recommendations for Dolutegravir Tablets in Adult Patients

Population	Recommended Dose
Treatment-naïve or treatment-experienced INSTI-naïve or virologically suppressed (HIV-1 RNA <50 copies per mL) adults switching to dolutegravir plus rilpivirine*	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1) or cytochrome P450 (CYP3A) inducers (see Drug Interactions (7.2, 7.3))	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance† (see Microbiology (12-4))	50 mg twice daily

*Rilpivirine dose is 25 mg once daily for those switching to dolutegravir plus rilpivirine.
*Alternative combinations that do not include metabolic inducers should be considered where possible (see **Drug Interactions** (7-3)).

2.3 General Dosing and Administration Instructions for Pediatric Patients
Do not interchange dolutegravir tablets and dolutegravir tablets for oral suspension on a milligram-per-milligram basis due to differing pharmacokinetic profiles (see **Warnings and Precautions** (5.6), **Clinical Pharmacology** (12-3)). If switching from the tablets for oral suspension to the tablets, follow the recommended dosage in Table 4.

2.5 Recommended Dose in Pediatric Patients Weighing 14 kg or Greater
For pediatric patients weighing 14 kg or greater (treatment-naïve or treatment-experienced, but naïve to INSTI treatment) and in pediatric patients weighing 14 kg or greater (see **Pharmacokinetics** (12-3)).

• Dolutegravir tablets for oral use (Table 4)

Table 4. Recommended Dose of Dolutegravir Tablets in Pediatric Patients Weighing 14 kg or Greater

Body Weight	Dolutegravir Tablets	
	Daily Dose*	Number of Tablets
14 kg to less than 20 kg	40 mg once daily	4 × 10-mg
20 kg and greater	50 mg once daily	1 × 50-mg

* If certain UGT1A1 or CYP3A inducers are coadministered, then administer dolutegravir tablets twice daily (see **Drug Interactions** (7.2, 7.3)).

2.6 Additional Administration Instructions
Administer dolutegravir tablets with or without food.

3 DOSE FORMS AND STRENGTHS
Dolutegravir Tablets:
Each 50 mg tablet contains 50 mg of dolutegravir (as dolutegravir sodium). Tablets are pink, round, biconvex, film coated tablet debossed with "14" on one side and "D" on the other side.

CONTRAINDICATIONS
Dolutegravir tablets are contraindicated in patients:

- with previous hypersensitivity reaction to dolutegravir (see **Warnings and Precautions** (5.1));
- receiving dolutegravir due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events (see **Drug Interactions** (7)).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions
Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of subjects receiving dolutegravir in Phase 3 clinical trials. Discontinue dolutegravir and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with dolutegravir or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. Dolutegravir is contraindicated in patients who have experienced a previous hypersensitivity reaction to dolutegravir.

5.2 Hepatotoxicity
Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir (see **Adverse Reactions** (6.1)). The elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver failure have been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with TRUVADA (emtricitabine, dolutegravir, and lamivudine). Monitoring for hepatotoxicity is recommended.

5.3 Embryo-Fetus Toxicity
An ongoing observational study showed an association between dolutegravir and an increased risk of neural tube defects when dolutegravir was administered at time of conception and in early pregnancy. As there is limited understanding of the association of reported types of neural tube defects with dolutegravir use, inform adolescents and adults of childbearing potential, including those actively trying to become pregnant, about the potential increased risk of neural tube defects with dolutegravir. Assess the risks and benefits of dolutegravir and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester (see *Use in Specific Populations* (8.1, 8.3)).

Pregnancy testing before initiation of dolutegravir in adolescents and adults of childbearing potential to exclude use of dolutegravir during the first trimester of pregnancy (see **Dosage and Administration** (2.1)).

Initiation of dolutegravir is not recommended in adolescents and adults actively trying to become pregnant unless there is no suitable alternative (see *Use in Specific Populations* (8.1, 8.3)).

Adolescents and adults of childbearing potential should be counseled on the consistent use of effective contraception (see *Use in Specific Populations* (8.1, 8.3)).

Dolutegravir may be considered during the second and third trimesters of pregnancy if the expected benefit justifies the potential risk to the pregnant woman and the fetus.

5.4 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions
The concomitant use of dolutegravir and other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of virologic response (see **Contraindications** (4), **Drug Interactions** (7-3)).

• Loss of therapeutic effect of dolutegravir and possible development of resistance.
• Possibly clinically significant adverse reactions from greater exposures of concomitant drugs.

For concomitant drugs for which the interaction can be mitigated, please see Table 8 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with dolutegravir; review concomitant medications during therapy with dolutegravir; and monitor for the adverse reactions associated with the concomitant drugs.

5.5 Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including dolutegravir. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection), cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and management.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

5.6 Different Formulations Are Not Interchangeable
Dolutegravir tablets and dolutegravir tablets for oral suspension are not bioequivalent and are not interchangeable on a milligram-per-milligram basis (see **Clinical Pharmacology** (12-3)). If a pediatric patient switches from one formulation to the other, the dose must be adjusted for the new dosage formulation (see **Dosage and Administration** (2-3)). Incorrect dosing of a given formulation may result in underdosing and loss of therapeutic effect and possible development of resistance or clinically significant adverse reactions associated with greater exposure of dolutegravir.

6 ADVERSE REACTIONS
The following serious adverse drug reactions are discussed in other sections of the labeling:

- Hypersensitivity reactions (see **Warnings and Precautions** (5.1)).
- Hepatotoxicity (see **Warnings and Precautions** (5.2)).
- Immune Reconstitution Syndrome (see **Warnings and Precautions** (5.5)).

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in routine clinical practice.

Clinical Trials Experience in Adult Subjects
Treatment-Naïve Subjects: The safety assessment of dolutegravir in HIV-1-infected treatment-naïve subjects is based on the analysis of data from 2 international, multicenter, open-label, double-blind trials, SPRING-2 (NMG13080) and SINGLE (NMG14467) and data from the international, multicenter, open-label FLAMINGO (NMG14915) trial.

In SPRING-2, 822 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) treatment (either abacavir sulfate and lamivudine [EPZCOM] or emtricitabine/tenofovir [TRUVADA]). There were 803 subjects included in the efficacy and safety analyses. Through 96 weeks, the rate of adverse events leading to discontinuation was 2% in both treatment arms.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg with fixed-dose abacavir sulfate and lamivudine (EPZCOM) once daily or fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA) once daily (study treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rates of adverse events leading to discontinuation were 4% in subjects receiving dolutegravir 50 mg once daily + EPZCOM and 14% in subjects receiving ATRIPLA once daily.

Table 5. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

Laboratory Parameter Preferred Term	SPRING-2		SINGLE	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir 50 mg + EPZCOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)

ALL: All laboratory parameters. ULN: Upper limit of normal.

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ULN = Upper limit of normal.

Table 6. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

Laboratory Parameter Preferred Term	SPRING-2		SINGLE	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir 50 mg + EPZCOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)

HDL cholesterol (mg/dL): 8.1, 2.0, 2.3, 5.4, 2.7
LDL cholesterol (mg/dL): 2.0, 10.3, 16.0, 14.6
Triglycerides (mg/dL): 6.7, 6.6, 13.6, 31.9

HDL = high density lipoprotein; LDL = low density

* Iliopsoas tendinitis or ligament-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SPRING-2, and in SINGLE, Dolutegravir + EPZCOM = 30 and ATRIPLA = 27). Ninety-four subjects initiated a lipid-lowering agent post-baseline, their last tested on-treatment values (prior to starting the agent) were used regardless of whether they discontinued the agent (SPRING-2: Dolutegravir = 9, raltegravir = 13; SINGLE: Dolutegravir + EPZCOM = 36, ATRIPLA = 38).

Laboratory abnormalities observed in the FLAMINGO trial were generally consistent with observations in SPRING-2 and SINGLE.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: Laboratory abnormalities observed in SALLING were generally similar compared with observations seen in the treatment-naïve (SPRING-2 and SINGLE) trials.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: The most common treatment-emergent laboratory abnormalities (greater than 5% for Grades 2 to 4 combined) observed in VIKING-3 at Week 48 were elevated ALT (9%), AST (8%), creatine kinase (10%), creatine kinase (6%), hyperglycemia (14%), and lipases (10%). Two percent (4 of 183) of subjects had a Grade 3 or higher treatment-emergent laboratory abnormality (hyperglycemia), with neutropenia (2% of 183) being the most frequently reported.

Virologically Suppressed Adults: Laboratory abnormalities observed in SWORD-1 and SWORD-2 were generally similar compared with observations seen in the other Phase 3 trials.

Hepatitis B and/or Hepatitis C Virus Co-infection: In Phase 3 trials, subjects with hepatitis B and/or C virus co-infection were permitted to enroll in these studies if their baseline liver chemistry tests did not exceed 5 times the upper limit of normal. Overall, the safety profile in subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects without hepatitis

• Dolutegravir tablets: 50 mg (3)

CONTRAINDICATIONS
• Previous hypersensitivity reaction to dolutegravir. (4)
• Coadministration with dofetilide. (4)

WARNINGS AND PRECAUTIONS
• Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported. Discontinue dolutegravir and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop, as a delay in stopping treatment may result in a life-threatening reaction. (5.1)

• Hepatotoxicity has been reported in patients receiving dolutegravir-containing regimens. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations. Monitoring for hepatotoxicity is recommended. (5.2)

• Embryo-fetus toxicity may be associated with use of dolutegravir during pregnancy. Assess the risks and benefits of dolutegravir and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy, or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. Adolescents and adults of childbearing potential should be counseled on the consistent use of effective contraception. (2.1, 5.3, 8.1, 8.3)

• Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.5)

• Dolutegravir tablets and dolutegravir tablets for oral suspension are not interchangeable. (2.3, 5.6)

ADVERSE REACTIONS
The most common adverse reactions of moderate to severe intensity and incidence at least 2% (in those receiving dolutegravir in any one adult trial) are insomnia, fatigue, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
• Refer to the full prescribing information for important drug interactions with dolutegravir. (4, 7)
• Drugs that are metabolic inducers may decrease the plasma concentrations of dolutegravir. (7.2, 7.3)
• Dolutegravir should be taken 2 hours before or 2 hours after taking calcium-containing antacids or laxatives, sucralfate, and oral supplements containing iron or calcium, or buffered medications. When taken with food, dolutegravir and supplements containing calcium or iron can be taken at the same time. (7.3)

USE IN SPECIFIC POPULATIONS
• Pregnancy: Assess the risks and benefits of dolutegravir and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. (2.1, 5.3, 8.1, 8.3)
• Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
• Females and males of reproductive potential: Pregnancy testing is recommended in adolescents and adults of childbearing potential. Patients should be counseled on the consistent use of effective contraception. (8.1, 8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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8 USE IN SPECIFIC POPULATIONS

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Treatment-emergent adverse reactions of moderate to severe intensity observed in at least 2% of subjects in either treatment arm in SPRING-2 and SINGLE trials are provided in Table 5. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should be made to differing trial designs.

Table 5. Treatment-Emergent Adverse Reactions of Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

System Organ Class/ Preferred Term	SPRING-2		SINGLE	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir 50 mg + EPZCOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)

Psychiatric
Insomnia <1% <1% 3% 3%
Depression <1% <1% <1% 2%
Anxiety <1% <1% <1% 2%

Nervous System
Dizziness <1% <1% <1% 2%
Headache <1% <1% <1% 5%

Gastrointestinal
Diarrhea <1% <1% <1% 2%
Nausea <1% <1% <1% 2%

Skin and Subcutaneous Tissue
Rash <1% <1% <1% 6%

General Disorders
Fatigue <1% <1% 2% 2%

Ear and Labyrinth
Vertigo 0 <1% 0 2%

*Includes pooled terms: rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and drug eruption.

In addition, Grade 1 insomnia was reported by 14% and less than 1% of subjects receiving dolutegravir and raltegravir, respectively, in SPRING-2; whereas in SINGLE the rates were 7% and 4% for dolutegravir and ATRIPLA, respectively. These events were not treatment-limited.

In a multicenter, open-label trial (FLAMINGO), 243 subjects received dolutegravir 50 mg once in twice 242 subjects who received darunavir 800 mg twice daily, both in combination with investigator-selected NRTI background regimen (either EPZCOM or TRUVADA). There were 464 subjects included in the efficacy and safety analyses. Through 96 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving dolutegravir and 6% in subjects receiving darunavir/ritonavir. The adverse reactions observed in FLAMINGO were generally consistent with those seen in SPRING-2 and SINGLE.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In an international, multicenter, double-blind trial (NMG11762, SALLING), 719 HIV-1-infected, antiretroviral treatment-naïve subjects were randomized and received either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving dolutegravir 50 mg once daily + background regimen and 4% in subjects receiving raltegravir 400 mg twice daily + background regimen.

The only treatment-emergent adverse reaction of moderate to severe intensity with at least 2% frequency in either treatment group was diarrhea, 2% (6 of 354) in subjects receiving dolutegravir 50 mg once daily + background regimen and 1% (5 of 361) in subjects receiving raltegravir 400 mg twice daily + background regimen.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: In a multicenter, open-label, single-arm trial (NMG12574, VIKING-3), 183 HIV-1-infected, antiretroviral treatment-experienced adults with virological failure and current or history of evidence of raltegravir and/or efavirenz resistance received dolutegravir 50 mg twice daily with the current failing background regimen for 7 days and with optimized background therapy from Day 8. The rate of adverse events leading to discontinuation was 4% of subjects at Week 48.

Treatment-emergent adverse reactions in VIKING-3 were generally similar compared with observations with the 50 mg once-daily dose in adult Phase 3 trials.

Virologically Suppressed Subjects: The adverse reactions observed for dolutegravir plus rilpivirine in the HIV-1-infected, virologically suppressed subjects switching from their current antiretroviral regimen to dolutegravir plus rilpivirine, were consistent with the adverse reaction profiles from and similar to the individual components when administered with

Drug	Dose	n	1.00	0.98	0.99
Methadone	50 mg twice daily	11	(0.94 to 1.06)	(0.91 to 1.06)	(0.91 to 1.07)
Midazolam	25 mg once daily	10	—	0.95 (0.79 to 1.15)	—
Nevapiprom	50 mg	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine	50 mg 25 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (1.00 to 1.16)	1.17 (1.07 to 1.28)
Sofosbuvir	50 mg once daily	24	0.88 (0.80 to 0.98)	0.92 (0.85 to 0.99)	NA
Metabolite (GS-331007)	50 mg once daily	24	0.91 (0.83 to 1.00)	0.99 (0.97 to 1.01)	0.99 (0.97 to 1.01)
Tidagrolone	50 mg	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)
Velgavirine	50 mg 100 mg once daily	24	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)

* The number of subjects represents the maximum number of subjects that were evaluated.

Table 12. Summary of Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (95% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C _{max}	AUC	C _r or C _{tr}
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.34 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/rilpivirine 300/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/rilpivirine 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Ebavirenz/raltegravir 50/200 mg once daily	50 mg single dose	12	1.11 (1.05, 1.40)	1.18 (1.00, 1.34)	1.41 (0.95, 1.36)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/rilpivirine 200 mg + 600/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/rilpivirine 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.72 (1.13 to 1.45)
Fosamprenavir/rilpivirine 700 mg/100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.75 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/rilpivirine 400/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.08 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Tipranavir/rilpivirine 500/200 mg twice daily	50 mg once daily	14	0.54 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Atacizid (MAALOX) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Atacizid (MAALOX) 2 h after dolutegravir	50 mg single dose	16	0.92 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.78 (0.56 to 0.85)
Calcium carbonate 1200 mg simultaneous administration (fasted)	50 mg single dose	12	0.58 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.96 (0.62 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16 ^a	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Dactarone 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	0.81 (0.61 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin 600 mg once daily	50 mg once daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin 900 mg once daily	50 mg once daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Ribavirin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

* The number of subjects represents the maximum number of subjects that were evaluated.
^a Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.
^b Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.

12.4 Microbiology

Mechanism of Action
Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. Strand transfer inhibitor class: Strand transfer inhibitor using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC₅₀ values of 2.7 nM and 12.6 nM.

Antiviral Activity in Cell Culture
Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC₅₀ values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and M1 cells. Dolutegravir exhibited antiviral activity against 13 clinical HIV-1 isolates with a mean EC₅₀ value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M clades A, B, C, D, E, F, and G, and 3 in group D) with EC₅₀ values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC₅₀ values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Antiviral Activity in Combination with Other Antiviral Agents
The antiviral activity of dolutegravir was not antagonistic when combined with the INSTI, raltegravir; non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz or nevirapine; the NRTIs, abacavir or stavudine; the protease inhibitors (PIs), darunavir or lopinavir; the CCR5 co-receptor antagonist, maraviroc; or the fusion inhibitor, enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HIV reverse transcriptase inhibitor, adinavir; or inhibited by the antiviral, ribavirin.

Resistance
Cell Culture: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and HIV-1 clinical isolates E202, G118R, S153F or Y, G135R or R253K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold. Passage of mutant viruses containing the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutions included Y19A, E158K, G140S, and M154I. Passage of mutant viruses containing both G146S and Q148H selected for L74M, E92Q, and N155H.

Treatment-Naïve Subjects: No subjects who received dolutegravir 50-mg once-daily in the treatment-naïve trials SPRING-2 (96 weeks) and SINGLE (144 weeks) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 12) with HIV-1 RNA greater than 400 copies per mL at baseline and having resistance data. Two virologic failure subjects in SINGLE had treatment-emergent G163E/R and G130S/E integrase substitutions at Week 84 and Week 108, respectively, and 1 subject with 275 copies per mL HIV-1 RNA had a treatment-emergent Q157/P integrase substitution detected at Week 24. None of these subjects had a corresponding decrease in dolutegravir susceptibility. No treatment-emergent genetic resistance to the background regimen was observed in the dolutegravir arm in either the SPRING-2 or SINGLE trials. No treatment-emergent primary resistance substitutions were observed in either treatment group in the FLAMINGO trial through Week 96.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In the dolutegravir arm of the SAILING trial for treatment-experienced and INSTI-naïve subjects (n = 354), simultaneous integrase substitutions were observed in 1 of 28 (21%) subjects who had virologic failure and resistance data. In 5 of the 6 subjects' isolates emergent INSTI substitutions included L74L/M, Y95D/L, V151V (n = 1 each), and R263K (n = 2). The change in dolutegravir phenotypic susceptibility for these 5 corresponding isolates was less than 2-fold. One subject isolate had pre-existing raltegravir resistance substitutions E158A, G146S, and Q148H at baseline and had additional emergent INSTI-resistance substitutions Y19A and E158K with a threefold 148-fold reduction in dolutegravir susceptibility at baseline. In the comparator raltegravir arm, 21 of 49 (43%) subjects with post-baseline resistance data had evidence of emergent INSTI-resistance substitutions (L74M, E92Q, Y19A, E158K, G140S, Y143R/K, Q148R/K, V151I, N155H, E157D, and G163K/R) and raltegravir phenotypic resistance.

Virologically Suppressed Subjects: SWOR-D-1 and SWOR-D-2 are identical trials in virologically suppressed subjects receiving 2 NRTIs plus either an INSTI, an NNRTI, or a PI, that switched to dolutegravir plus rilpivirine (n = 513) or remained on their current antiretroviral regimen (n = 511). In the pooled SWOR-D-1 and SWOR-D-2 trials, 12 subjects (2 in SWOR-D-1 and 5 in SWOR-D-2) had confirmed virologic failure (HIV-1 RNA greater than 200 copies/mL) while receiving dolutegravir plus rilpivirine at any time through Week 148. Ten of the confirmed virologic failures had post-baseline resistance data, with 6 isolates showing evidence of rilpivirine resistance, and 2 with evidence of dolutegravir resistance substitutions. Six isolates showed genotypic and/or phenotypic resistance to rilpivirine with emergent NNRTI-resistance substitutions E158E/R (rilpivirine 1.6-fold change), M230M/L (rilpivirine 2-fold change), L100L/L, K101D, and E158A (rilpivirine 4.1-fold change), K101K/E (rilpivirine 1.2-fold change), K101K/E, M230M/L (rilpivirine 2-fold change), and L100L/M, M230M/L (rilpivirine 31-fold change). In addition, 1 virologic failure subject had NNRTI-resistance substitutions K103H and V179I at Week 88 with rilpivirine phenotypic fold change of 5.2 but had no baseline sample.

One virologic failure isolate had emergent INSTI-resistance substitution V151V/I present post-baseline with baseline INSTI-resistance substitutions N155N/H and G163G/R (by exploratory HIV proviral DNA archive sequencing); no integrase phenotypic data were available for this isolate at virologic failure. One other subject had the dolutegravir resistance substitution G193E at baseline and virologic failure, but no detectable phenotypic change (fold-change = 1.0) at Week 24.

No resistance-associated substitutions were observed for the other 2 subjects meeting confirmed virologic failure in the comparative current antiretroviral regimen arms at Week 48.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: VIKING-3 examined the efficacy of dolutegravir 50 mg twice daily plus optimized background therapy in subjects with prior or current virologic failure on an INSTI- (raltegravir or atazanavir) containing regimen. Use of dolutegravir in INSTI-experienced patients should be guided by the number and type of baseline INSTI substitutions. The efficacy of dolutegravir 50 mg twice daily is reduced in patients with an INSTI-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions, including T66A, L74L/M, E158K/KT, G140S/A/C, Y143R/C, E157D, G163S/E/K/Q, or G193E/R.

Response by Baseline Genotype
Of the 152 subjects with baseline data, 30% harbored virus with a substitution at Q148, and 32% had no primary INSTI-resistance substitutions (T66A/V, E92Q/V, Y143R/C, Q148H/R/K, or N155H) at baseline, but had historical genotypic evidence of INSTI-resistance substitutions, phenotypic evidence of integrase or raltegravir resistance, or genotypic evidence of INSTI-resistance substitutions at screening.

Response rates by baseline genotype were analyzed in an "as-treated" analysis of Week 48 (n = 175) (Table 13). The response rate at Week 48 to dolutegravir-containing regimens was 47% (24 of 51) when Q148 substitutions were present at baseline; Q148 was always present with additional INSTI-resistance substitutions (see Table 13). In addition, a diminished virologic response rate of 40% (6 of 15) was observed when the substitution E157D or Y was present at baseline with other INSTI-resistance substitutions but without a Q148H or R substitution.

Baseline Genotype	Week 48 (<50 copies/mL) n = 176
Overall Response	66% (116/175)
No Q148 substitution ^a	74% (92/124)
Q148H/R + G140S/A/C without additional INSTI-resistance substitution ^b	61% (17/28)
Q148H/R + ≥2 INSTI-resistance substitutions ^b	29% (6/21)

INSTI = integrase strand transfer inhibitor.
^a Includes INSTI-resistance substitutions Y143R/C/H and N155H.
^b INSTI-resistance substitutions included T66A, L74M, E158K/KT, G140S/A/C, Y143R/C, E157D, G163S/E/K/Q, or G193E/R. Two additional subjects with baseline genotypes of Q148R/P plus L74L/M (virologic failure) and Q148R plus E158K (responder).
^c The most common pathway with Q148H/R + greater than or equal to 2 INSTI-resistance substitutions had Q148H-G140S-E158K substitutions (n = 16).

Response by Baseline Phenotype
Response rates by baseline phenotype were analyzed in an as-treated analysis using all subjects with available baseline phenotypes through Week 48 (n = 163) (see Table 14). These baseline phenotype groups are based on subjects enrolled in VIKING-3 and are not meant to represent definitive clinical susceptibility points for dolutegravir. The data are provided to guide clinicians on the likelihood of virologic success based on pretreatment susceptibility to dolutegravir in INSTI-naïve subjects.

Baseline Dolutegravir Phenotype (Fold-Change from Reference)	Response at Week 48 (<50 copies/mL) Subset n = 163
Overall Response	64% (104/163)
<3-fold change	72% (83/116)
3- <10-fold change	53% (18/34)
≥10-fold change	23% (3/13)

Integrase Strand Transfer Inhibitor Treatment-Emergent Resistance
There were 50 subjects with virologic failure on the dolutegravir twice-daily regimen in VIKING-3 with HIV-1 RNA greater than 400 copies per mL at the failure timepoint, Week 48 or beyond, or the last timepoint on trial. Thirty-nine subjects with virologic failure had resistance data that were used in the Week 48 analysis. In the Week 48 resistance analysis 85% (33 of 39) of the subjects with virologic failure had treatment-emergent INSTI-resistance substitutions in their isolates. The most common treatment-emergent INSTI-resistance substitution was Y19A. Other frequently emergent INSTI-resistance substitutions included E158K, G140S, or Y143R. R or K, G140S, Q148R, R or K, M154I, or N155H. Substitutions E92Q, Y143R or C, H147Q, V151A, and E157D/E each emerged in 1 to 3 subjects' isolates. At failure, the median dolutegravir fold-change from reference was 6.1-fold (range 0.75 to 209) for isolates with emergent INSTI.

In VIKING-4 (ING116529), 30 subjects with current virological failure on an INSTI-containing regimen and genotypic evidence of INSTI-resistance substitutions at screening were randomized to receive either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days and then all subjects received open-label dolutegravir plus optimized background regimen from Day 8. Virologic responses at Week 48 by baseline genotypic and phenotypic INSTI-resistance categories and the INSTI-resistance-associated substitutions that emerged on dolutegravir treatment in VIKING-4 were consistent with those seen in VIKING-3.

Cross-Resistance
Site-Directed Integrase Strand Transfer Inhibitor-Resistant Mutant HIV-1 and HIV-2 Strains: The susceptibility of dolutegravir was tested against 60 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) and 6 INSTI-resistant site-directed mutant HIV-2 viruses. The single INSTI-resistance substitutions T66K, H151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, Y97A/G140S/Q148, and substitutions at E136G/H/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153S/W155H, V163G and E92Q/Y97A/N155H/S163G conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent antiviral activity against 2 NNRTI-resistant, 3 NRTI-resistant, and 2 PI-resistant HIV-1 mutant clones compared with the wild-type strain.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg per kg, and rats were administered doses of up to 50 mg per kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 14 times higher than those in humans at the maximum recommended dose. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 10 times and 15 times higher in males and females, respectively, than those in humans at the maximum recommended dose.

Mutagenesis
Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the *in vivo* rodent micronucleus assay.

Impairment of Fertility
In a study conducted in rats, there were no effects on mating or fertility with dolutegravir up to 1,000 mg per kg per day. This dose is associated with an exposure that is approximately 24 times higher than the exposure in humans at the maximum recommended dose.

14 CLINICAL STUDIES
14.1 Description of Clinical Studies
The efficacy and safety of dolutegravir was evaluated in the studies summarized in Table 15.

Table 15. Trials Conducted with Dolutegravir in HIV-1-Infected Subjects

Population	Trial	Trial Arms	Timepoint (Week)
Adults: Treatment-naïve	SPRING-2 (ING13086) (NCT0127824)	Dolutegravir + 2 NRTIs (n = 403)	96
		Raltegravir + 2 NRTIs (n = 405)	
Treatment-naïve Subjects	SINGLE (ING114467) (NCT01263015)	Dolutegravir + EPZICOM (n = 414)	144
		ATRIPLA (n = 419)	
Treatment-naïve Subjects	FLAMINGO (ING114915) (NCT01499629)	Dolutegravir + NRTI BR (n = 243)	96
		Darunavir + NRTI BR (n = 242)	
Treatment-experienced, INSTI-naïve	SAILING (ING11782) (NCT01251516)	Dolutegravir + BR (n = 354) Dolutegravir + BR (n = 361)	48
INSTI-experienced	VIKING-3 (ING112574) (NCT01320847)	Dolutegravir + OBT (n = 183)	48
Virologically suppressed	SWOR-D-1 (NCT02429791) SWOR-D-2 (NCT02422797)	Pooled treatment: Dolutegravir + Rilpivirine (n = 513) CAR (n = 511)	48
Pediatrics:	IMPACT P1093 (NCT01302874)	Dolutegravir tablets or dolutegravir tablets for oral suspension + BR (n = 75)	24

14.2 Adult Subjects
Treatment-Naïve Subjects
In SPRING-2, 822 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual NRTI treatment (either abacavir sulfate and lamivudine [EPZICOM] or emtricitabine/tenofovir [TRUVADA]). There were 808 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 36 years, 13% female, 15% non-white, 11% had hepatitis B, and/or C virus co-infection, 2% were CDC Class C (AIDS), 28% had HIV-1 RNA greater than 100,000 copies per mL, 48% had CD4+ cell count less than 350 cells per mm³, and 39% received EPZICOM; these characteristics were similar between treatment groups.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily with fixed-dose abacavir sulfate and lamivudine (EPZICOM) or fixed-dose emtricitabine/tenofovir (ATRIPLA). At baseline, the median age of subjects was 35 years, 16% female, 32% non-white, 7% had hepatitis B and/or C virus co-infection was excluded, 4% were CDC Class C (AIDS), 32% had HIV-1 RNA greater than 100,000 copies per mL, and 53% had CD4+ cell count less than 350 cells per mm³; these characteristics were similar between treatment groups.

Outcomes for SPRING-2 (Week 96 analysis) and SINGLE (Week 144 open-label phase analysis which followed the Week 96 double-blind phase) are provided in Table 16. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 16. Virologic Outcomes of Randomized Treatment in SPRING-2 at Week 96 and SINGLE at Week 144 (Snapshot Table)

	SPRING-2 Week 96		SINGLE Week 144	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 405)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir 50 mg Once Daily + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)
HIV-1 RNA <50 copies/mL	82%	78%	71%	63%
Treatment difference ^a	4.9% (95% CI: -0.6%, 10.3%) ^b			
Virologic nonresponse	5%	10%	10%	7%
Data in window not <50 copies/mL	1%	3%	4%	<1%
Discontinued for lack of efficacy	<1%	3%	3%	3%
Discontinued for other reasons	<1%	3%	3%	4%
Change in ART regimen	<1%	<1%	0	0
No virologic data	12%	12%	18%	30%
Reasons	2%	2%	4%	14%
Discontinued study/drug due to adverse event or death ^c	8%	9%	12%	13%
Discontinued study/drug for other reasons ^d	2%	<1%	2%	3%
Missing data during window but on study				

Plasma viral load (copies/mL)
<100,000 84% 83% 73% 64%
100,000-79% 79% 69% 61%

Gender
Male 84% 79% 72% 66%
Female 70% 68% 69% 48%

Race
White 83% 78% 72% 71%
African-American/African Heritage/Other 77% 75% 71% 47%

NRTI = nucleoside reverse transcriptase inhibitor

^a Adjusted for pre-specified stratification factors.
^b The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving dolutegravir and 86% in the raltegravir group, with a treatment difference of 2.8% and 95% CI of (-1.9%, 7.2%).
^c The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving dolutegravir and 81% in the ATRIPLA group, with a treatment difference of 7.4% and 95% CI of (2.5%, 12.2%).
^d Includes subjects who discontinued due to an adverse event or death at any time point if this resulted in no virologic data at treatment duration by the analysis window.
^e Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.