

Dolutegravir (DTG, Tivicay, Tivicay PD)(Last updated February 12, 2021; last reviewed February 12, 2021)

Formulations

Tablets:

Dispersible tablets for oral suspension [Tivicay PD] 5 mg

Film-coated tablets [Tivicay] 10 mg, 25 mg, 50 mg

Fixed-Dose Combination Tablets:

- [Dovato] Dolutegravir 50 mg/lamivudine 300 mg
- [Juluca] Dolutegravir 50 mg/rilpivirine 25 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents](#).

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

Dosing Recommendations

Neonate Dose:

- Dolutegravir (DTG) is not approved by the Food and Drug Administration (FDA) for use in neonates.

Pediatric and Adult Dose:

[Tivicay PD] Dolutegravir dispersible tablets

- **Infant (Aged ≥ 4 weeks and Weighing ≥ 3 kg) and Child and Adolescent Dose:** DTG dispersible tablets are approved by the FDA for use in pediatric patients who are treatment-naïve or treatment-experienced but naïve to integrase strand transfer inhibitor (INSTI) treatment:

Pediatric Body Weight	Recommended Dose ^a of Dolutegravir Dispersible Tablets	Number of 5 mg Tablets
3 kg to <6 kg	5 mg once daily	1
6 kg to <10 kg	15 mg once daily	3
10 kg to <14 kg	20 mg once daily	4
14 kg to <20 kg	25 mg once daily	5
≥ 20 kg	30 mg once daily	6

^a If certain uridine diphosphate glucuronyl transferase (UGT) 1A or cytochrome P450 (CYP) 3A inducers are coadministered, administer DTG dispersible tablets twice daily.

[Tivicay] Dolutegravir film-coated tablets

Child and Adolescent (Weighing ≥ 14 kg) and Adult Dose:

Selected Adverse Events

- Insomnia
- Headache
- Neuropsychiatric symptoms (i.e., depression and/or suicidal thoughts or actions), especially in patients with a history of psychiatric illness
- Rare cases of hypersensitivity reactions, including rash and drug reaction (or rash) with eosinophilia and systemic symptoms, constitutional symptoms, and organ dysfunction (including liver injury).

Special Instructions

- DTG may be taken without meals.
- DTG should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications.
- Fully disperse the dispersible tablets in 5 mL of drinking water (if using one or three tablets) or in 10 mL of drinking water (if using four, five, or six tablets) in the supplied cup; swirl the suspension so that no lumps remain. After full dispersion and within 30 minutes of mixing, administer the oral suspension. Rinse the dosing cup with a small amount of water and give this additional water to the child to ensure the child takes the full dose and no medication

- For use in patients who are treatment-naïve or treatment-experienced but naïve to INSTI treatment.
- Do not use DTG film-coated tablets in patients weighing <14 kg.
- **DTG film-coated tablets and DTG dispersible tablets are not bioequivalent and are not interchangeable on a milligram-per-milligram basis. Each formulation has different doses.**

Dosing of film-coated tablets for pediatric patients weighing ≥ 14 kg who can swallow tablets:

Pediatric Body Weight	Recommended Dose ^a of Dolutegravir Film-Coated Tablets	Number of Tablets
14 kg to <20 kg	40 mg once daily	4 x 10 mg
≥ 20 kg	50 mg once daily	1 x 50 mg

^a If certain UGT1A or CYP3A inducers are coadministered, administer DTG tablets twice daily.

Some infants may have received raltegravir as presumptive HIV therapy prior to diagnosis. These infants and other infants and children with HIV who have received INSTIs are candidates to switch to once-daily DTG if they are virologically suppressed or have no mutations associated with resistance to INSTIs.

[Dovato] Dolutegravir/Lamivudine

Adult Dose:

- One tablet once daily with or without food as a complete regimen in antiretroviral (ARV)-naïve adults with no known mutations associated with resistance to the individual components of Dovato.
- Dovato is not approved by the FDA or recommended by the Panel for use in children or adolescents as a complete regimen. However, it could be used as part of a three-drug regimen in patients who meet the minimum body weight requirements for each component drug (see the Simplification of Treatment section below).

[Juluca] Dolutegravir/Rilpivirine

Adult Dose:

- One tablet once daily with a meal as a complete regimen to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months, with no history of treatment failure and no known mutations

- remains in the dosing cup.
- DTG dispersible tablets may be swallowed whole (if more than one tablet is required, swallow one tablet at a time to reduce the risk of choking).
- No data exist regarding dispersion in breast milk or any other vehicle.
- In patients who have difficulty swallowing tablets whole, 50 mg tablets may be either split into halves followed by immediate ingestion of **both halves** of the tablet, or crushed and added to a small amount of semisolid food or liquid, all of which should be consumed **immediately**.¹
- The efficacy of DTG 50 mg twice daily is reduced in patients with certain combinations of INSTI-resistance mutations (see the Resistance section below).
- Screen patients for hepatitis B virus (HBV) infection before using FDC tablets that contain lamivudine (3TC). Severe acute exacerbations of HBV can occur after discontinuation of 3TC. Patients with HBV/HIV coinfection who receive Dovato will require additional treatment for chronic HBV infection.

Metabolism/Elimination

- UGT1A1 and CYP3A substrate. Drugs that induce these enzymes and transporters may decrease plasma concentrations of DTG. Drugs that inhibit these enzymes may increase DTG plasma concentrations.

Dolutegravir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Because of a lack of data, DTG **is not recommended** for use in patients with severe hepatic impairment.
- **FDC tablets containing ABC or 3TC should not be used in patients with impaired hepatic function**

Dolutegravir Dosing in Patients with Renal Impairment:

- DTG decreases tubular secretion of creatinine and increases measured serum creatinine, without affecting glomerular filtration.
- No dose adjustment is required in INSTI-naïve patients with mild, moderate, or severe renal impairment, or in INSTI-experienced patients

associated with resistance to the individual components of Juluca.

- Juluca is not approved by the FDA or recommended by the Panel for use in children or adolescents as a complete regimen (see the Simplification of Treatment section below).

[Triumeq] Abacavir/Dolutegravir/Lamivudine

Child and Adolescent (Weighing ≥ 25 kg) and Adult Dose:

- One tablet once daily with or without food.
- For use in patients who are ARV-naïve or ARV-experienced (but INSTI-naïve) and who are not being treated with UGT1A1 or CYP3A inducers.
- See the [Abacavir section](#) for special instructions about testing for abacavir (ABC) hypersensitivity.
- The FDA-approved dose for pediatric patients weighing ≥ 40 kg is one tablet once daily, **but the Panel recommends this FDC can be used for patients ≥ 25 kg.**

- with mild or moderate renal impairment.
- Use DTG with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance < 30 mL/min), because DTG concentrations will be decreased. The cause of this decrease is unknown.
- **FDC tablets containing 3TC or ABC should not be used in patients who have creatinine clearance < 50 mL/min or who are on dialysis.**

Drug Interactions (see also the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#))

- **Metabolism:** Dolutegravir (DTG) is a uridine diphosphate glucuronyl transferase (UGT) 1A1 and cytochrome P450 (CYP) 3A substrate and may require dose adjustments when administered with UGT1A-modulating or CYP3A-modulating medications. Because etravirine (ETR) significantly reduces plasma concentrations of DTG, DTG **should not be administered** with ETR without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir, which counteract this effect on DTG concentrations. DTG **should not be administered** with nevirapine because of insufficient data on interactions between these drugs.
- Atazanavir (ATV) is an inhibitor of UGT1A1. In a recent pharmacologic survey of adult patients who were receiving DTG, patients who also received ATV had plasma concentrations of DTG that were twofold to fourfold higher than those of patients who received other antiretroviral (ARV) drugs.²
- Before administering DTG, clinicians should carefully review a patient's medication profile for potential drug interactions.

Major Toxicities

- **More common:** Insomnia and headache. Weight gain has also been reported in adults who received DTG **in clinical trials.** (see [Table 15h—Lyodystopies and Weight Gain](#)).
- **Less common (more severe):** Hypersensitivity reactions characterized by rash, constitutional symptoms, and sometimes organ dysfunction; neuropsychiatric symptoms, especially in patients with a history of psychiatric illness. Multiple post-marketing reports note that neuropsychiatric adverse effects (AEs) have occurred after initiation of DTG-based therapy in adults.^{3,4}
- **Immune reconstitution inflammatory syndrome (IRIS):** In retrospective observational studies, severe cases of IRIS that required hospitalization appeared to be more frequent in patients who presented with advanced disease and who initiated treatment with integrase strand transfer inhibitors (INSTIs),

particularly DTG.^{5,6} This phenomenon is presumed to be linked to the rapid decline in HIV RNA observed in patients receiving INSTI-based therapy.

- *Rare:* Hepatotoxicity has been reported; two cases of liver injury were presumed to be related to the use of DTG. One of these cases required liver transplantation.^{7,8}
- *Rare:* A single case of drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) has been reported.⁹
- *Rare:* In a prospective surveillance study of birth outcomes among pregnant women on antiretroviral therapy (ART) in Botswana, a very small significant increase in the risk of neural tube defects (NTDs) has been observed among infants born to women who were receiving DTG at the time of conception.^{10,11} Before patients become sexually active, pediatric and adolescent providers should discuss this very small potentially increased risk of NTDs with patients who are receiving or initiating DTG and their caregivers so that they can make informed decisions about its use (see [Appendix C. Antiretroviral Counseling Guide for Health Care Providers](#), [Teratogenicity](#) and [Recommendations for Use of Antiretroviral Drugs During Pregnancy](#) in the Perinatal Guidelines).

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a [list of updated resistance mutations](#) and the [Stanford University HIV Drug Resistance database](#) offers a discussion of each mutation.

The efficacy of DTG 50 mg twice daily is reduced in patients with the INSTI-resistance Q148 substitution plus two or more additional INSTI-resistance mutations.

Pediatric Use

Approval

DTG is approved by the Food and Drug Administration (FDA) for use, in combination with other ARV drugs, in **pediatric patients at least 4 weeks of age AND weighing at least 3 kg** who are treatment-naive or treatment-experienced but INSTI-naive (see [Appendix A, Table 2](#)). **Pediatric patients weighing ≥20 kg may take the DTG 50 mg film-coated tablets if they are able to swallow tablets.** These recommendations are based on pharmacokinetic (PK) and safety data from two ongoing clinical trials (IMPACT P1093 and ODYSSEY), which are described below. The combination tablet abacavir/dolutegravir/lamivudine (ABC/DTG/3TC; Triumeq) is approved by the FDA for use in children and adolescents weighing ≥40 kg, although the Panel recommends using it in children and adolescents weighing ≥25 kg (see [Appendix A, Table 2](#)). The combination tablets dolutegravir/rilpivirine (DTG/RPV; Juluca) and dolutegravir/lamivudine (DTG/3TC; Dovato) are not approved by the FDA for use in children or adolescents at the time of this review, and the Panel **does not recommend** using these drugs.

Formulation Differences: Film-Coated Tablet Compared to Dispersible Tablet

DTG is currently available as either film-coated tablets or as **dispersible tablets (tablets for oral suspension)**. The dispersible tablet has 60% to 80% greater bioavailability in adults than the film-coated tablet,¹² so recommended doses using the dispersible tablet cannot be directly compared to those using the film-coated tablets. The drug exposure provided by the 50-mg film-coated tablet is approximately equal to that of DTG 30 mg administered as dispersible tablets.

Efficacy and Pharmacokinetics

Clinical Trials in Pediatric Patients 4 Weeks to <18 years

IMPACT P1093 is an ongoing, **multinational**, open-label trial of DTG in children with HIV. **Results of PK, safety, and efficacy assessments have been reported sequentially for different age and weight cohorts as data became available; dosing recommendations have similarly been revised sequentially.**^{13–15} **Dosing**

recommendations that include the 25-mg film-coated tablets no longer exist.

Data from P1093 Cohort 1 (aged 12 years to <18 years) and Cohort 2 (6 years to <12 years) provide support for use of DTG film-coated tablets in pediatric patients ≥ 14 kg; Cohort 3 (2 to <6 years), Cohort 4 (6 months to <2 years), and Cohort 5 (4 weeks to <6 months) provide evidence supporting the use of DTG 5-mg dispersible tablets. Seventy-five study participants received the currently approved dose (determined by weight and age) of DTG film-coated tablets or dispersible tablets. These 75 participants ranged from 1 to 214 months; 59% were female, and 68% were Black or African American. Eighty percent of participants were treatment-experienced, but all were INSTI-naïve. Among these 75 patients who received either DTG film-coated tablets or DTG dispersible tablets, according to the approved dosing recommendations for their weight band, 42 received DTG for at least 48 weeks. At Week 48, 69% of participants achieved HIV RNA < 50 copies/mL, and 79% achieved HIV RNA < 400 copies/mL. The median CD4 T lymphocyte count (percent) increase from baseline to Week 48 was 141 cells/mm³ (7%). Overall, the safety profile in P1093 participants was comparable to that observed in adults, and both formulations were well tolerated by pediatric patients. The effectiveness observed in the trial was comparable to that of treatment-experienced adult subjects.¹⁶

Sixteen adolescents in Cohort 1 have remained on P1093 through 144 weeks, with 43% and 35% of participants achieving and maintaining HIV RNA levels < 400 copies/mL and < 50 copies/mL, respectively. Genotypic testing was available at the time of treatment failure for 6 of the 13 participants experiencing treatment failure; one of these adolescents developed DTG resistance.¹⁷

The ODYSSEY trial, conducted by the Pediatric European Network for the Treatment of AIDS (PENTA), enrolled both treatment-naïve and treatment-experienced pediatric patients in the European Union (EU), Thailand, and several African countries; this trial initially evaluated doses approved by the European Medicines Agency at the time the trial started. A total of 674 children aged < 18 years were enrolled; 282 children started DTG as first-line therapy, and 392 started DTG as second-line therapy.¹⁸ Nested PK substudies within ODYSSEY also evaluated simplified pediatric dosing that aligned with WHO-recommended weight bands. PK data are available from a cohort of children weighing > 25 kg who switched to the DTG 50-mg film-coated tablet. Data from another ODYSSEY cohort reported on children weighing 20 kg to < 25 kg who received either the DTG 50-mg film-coated tablet or 30 mg of DTG administered as six 5-mg dispersible tablets. Both of these doses achieved area-under-the-curve (AUC) and maximum plasma concentration (C_{\max}) values that were higher than adult PK reference values but still acceptable, and both doses achieved C_{trough} values that were similar to adult reference values.^{19,20} Long-term safety and effectiveness assessments in the ODYSSEY trial are ongoing.

Combined PK data from P1093 and ODYSSEY across all age/weight cohorts form the basis for the current FDA dose recommendations and are summarized in Table A. These data support administration of either 30 mg given as dispersible tablets or the 50 mg film-coated tablet in patients weighing ≥ 20 kg. In addition, modeling and simulations that included UGT1A1 maturation in infants were used to support the dose of DTG down to 4 weeks of age and 3 kg. Dosing in neonates is under investigation.

Pediatric Postmarketing Safety Studies

Additional long-term safety and efficacy data for this age/weight group come from a retrospective, multicenter French cohort study that evaluated 50 adolescents who initiated DTG-based ART. Of 17 adolescents who were virologically suppressed at the time of DTG-based treatment, 14 (82%) maintained suppression, and three had transient viral rebound prior to re-achieving a plasma viral load < 50 copies/mL. Of the 33 viremic adolescents who initiated DTG, 19 (58%) achieved sustained virologic success. Overall, 66% of patients achieved sustained virologic suppression, and 78% had undetectable plasma viral loads by the last study visit. Adolescents with virologic failure were more likely to be from sub-Saharan Africa and

Table A: Summary of Pharmacokinetic Parameters in Pediatric HIV-1-Infected Participants (Pooled Analyses for IMPAACT P1093 and ODYSSEY Trials)

Weight Band ^a	Dose ^b of DTG FCT or DTG DT	n	Pharmacokinetic Parameter Geometric Mean (%CV)		
			C _{max} (mcg/mL)	AUC _{0-24h} (mcg·h/mL)	C _{24h} (ng/mL)
3 kg to <6 kg	DTG DT 5 mg once daily	8	3.80 (34)	49.37 (49)	962 (98)
6 kg to <10 kg	DTG DT 15 mg once daily	17	5.27 (50)	57.17 (76)	706 (177)
10 kg to <14 kg	DTG DT 20 mg once daily	13	5.99 (33)	68.75 (48)	977 (100)
14 kg to <20 kg	DTG DT 25 mg once daily	19	5.97 (42)	58.97 (44)	725 (75)
20 kg to <25 kg	DTG DT 30 mg once daily	9	7.16 (26)	71.53 (26)	759 (73)
≥20 kg	DTG FCT 50 mg once daily	49	4.92 (40)	54.98 (43)	778 (62)
Adults	DTG FCT 50 mg once daily	6	3.67 (20)	53.6 (27)	1,110 (46)
Adults	DTG FCT 50 mg twice daily	6	4.15 (29)	75.1 (35)	2,120 (47)

^a Data are from two weight-band-based pharmacokinetic substudies in the ODYSSEY trial.

^b The bioavailability of DTG tablets for oral suspension is approximately 1.6-fold that of DTG film-coated tablets.

^c Adult pharmacokinetic data are based on population pharmacokinetic analyses from clinical trials.¹⁶

Key: AUC = area under the curve; C = plasma concentration; C_{max} = maximum plasma concentration; CV = coefficient of variation, DTG DT = dolutegravir dispersible tablets; DTG FCT = dolutegravir film-coated tablets

were more likely to have detectable viremia in the 6 months prior to DTG initiation. No resistance mutations emerged in patients with virologic failure, and only one patient discontinued DTG-based treatment because of a significant AE (dizziness and sleep disturbance).²¹

Another cohort of adolescents in Barcelona, Spain, received the fixed-dose combination (FDC) product ABC 600 mg/DTG 50 mg/3TC 300 mg (Triumeq). Of the 12 patients described, one received Triumeq for initial ART, six received Triumeq for treatment simplification, and five received Triumeq because of previous treatment failure. Nine of the 12 patients achieved or maintained viral suppression after switching to Triumeq; three patients failed to achieve suppression because of suboptimal adherence. Of note, patients complained about the size of the tablet, and six patients reported having to crush or split the tablet to swallow it (see [Appendix A, Table 2](#)).²²

Simplification of Treatment

Two trials in adults (SWORD-1 and SWORD-2) supported the approval of a DTG 50 mg/RPV 25 mg FDC tablet (Juluca) as a complete regimen for treatment simplification or maintenance therapy in selected patients. The two identical SWORD trials enrolled 1,024 virologically suppressed patients who had been on stable ART for at least 6 months and who had no history of treatment failure or evidence of resistance mutations. The participants were randomized either to receive DTG/RPV or to continue their suppressive ARV regimen. After 48 weeks of treatment, 95% of patients in both arms maintained HIV RNA levels <50 copies/mL.²³ After 52 weeks, the participants who had been randomized to continue their suppressive ARV regimen were switched to DTG/RPV. At 148 weeks, 84% of the early-switch patients and 90% of the late-

switch patients remained virologically suppressed, and only 11 patients receiving dual therapy met virologic failure criteria. No integrase inhibitor resistance was identified.²⁴ During the comparative randomized phase of the study, more AEs were reported and led to discontinuation in the DTG/RPV arm. In a subgroup of the SWORD study, small but statistically significant increases in hip and spine bone mineral density and bone turnover markers were observed in patients whose original ARV regimen contained tenofovir disoproxil fumarate (TDF).²⁵

The approval of DTG 50 mg/3TC 300 mg (Dovato) as a complete regimen was supported by data from two randomized, double-blind, controlled trials (GEMINI-1 and GEMINI-2) in ARV-naive adults with HIV. GEMINI-1 and GEMINI-2 are identical 148-week trials that enrolled a total of 1,433 adults with HIV who had plasma HIV RNA levels between 1,000 copies/mL and $\leq 500,000$ copies/mL at screening and no evidence of major resistance mutations or hepatitis B virus infection. Participants were randomized to receive either DTG plus 3TC or DTG plus 3TC/TDF. During 96 weeks of treatment, 86% of patients who received DTG plus 3TC and 89.5% of patients who received DTG plus 3TC/TDF achieved HIV RNA levels < 50 copies/mL. Patients receiving DTG plus 3TC had a lower rate of adverse drug reactions (19.6%) compared to those receiving DTG plus 3TC/TDF (25%).²⁶

Although neither Juluca nor Dovato is approved by the FDA for use in adolescents, the doses of the component drugs that make up these FDC tablets are approved for use in adolescents. The Panel usually endorses the use of adult formulations in adolescents, and these products may be appropriate for use in certain adolescents. However, because the strategy of treatment simplification has not been evaluated in adolescents who may have difficulty adhering to therapy, the Panel **does not currently recommend** using two-drug simplification regimens in adolescents and children until more data are available.

Crushing Film-Coated Tablets for Administration

Dispersible tablets are now considered the preferred formulation for pediatric patients < 20 kg, and film-coated tablets should not be used in children weighing < 14 kg. In patients who have difficulty swallowing whole tablets and in children weighing > 14 kg, when the preferred dispersible tablets are not available, the 10 mg and 50 mg tablets either may be split into halves followed by immediate ingestion of **both halves** of the tablet, or crushed and added to a small amount of semisolid food or liquid, all of which should be consumed **immediately**.¹ Crushing and mixing film-coated tablets would not be expected to adversely impact the product's pharmaceutical quality and, therefore, would not be expected to alter the intended clinical effect. This conclusion is based on the physicochemical and PK characteristics of the active ingredient and the *in vitro* dissolution behavior of the film-coated tablets in water. In healthy adults, the use of crushed tablets resulted in slightly higher exposures than the use of whole tablets.²⁷ No information exists on the impact of splitting or crushing film-coated tablets on palatability. Some case reports describe DTG-containing film-coated tablets' being crushed and successfully administered via orogastric tube²⁸ or nasogastric tube,²⁹ and it is expected that the dispersible tablets may also be administered similarly. If DTG is administered via enteral tube, care should be taken to disperse the tablets completely and flush the tube to avoid clogging.

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