Dolutegravir (DTG, Tivicay, Tivicay PD)

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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
- [Triumeq PD] Abacavir 60 mg/dolutegravir 5 mg/lamivudine 30 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of Appendix A: Pediatric Antiretroviral Drug Information 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

All formulations and FDCs of dolutegravir (DTG) are U.S. Food and Drug Administration (FDA)–approved for use in treatment-naive or treatment-experienced pediatric, adolescent, and adult patients naive to the integrase strand transfer inhibitor (INSTI) drug class. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV endorses the use of DTG as appropriate for some children with prior INSTI use (see Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy and Recognizing and Managing Antiretroviral Treatment Failure in Management of Children Receiving Antiretroviral Therapy).

Neonate Dose

- DTG is not approved by the FDA for use in neonates.

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 (HSRs), including rash and DRESS (drug reaction [or rash] with eosinophilia and systemic symptoms), constitutional symptoms, and organ dysfunction (including liver injury)

Special Instructions

- DTG may be taken with or without food.
- 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.

[Tivicay PD] DTG Dispersible Tablets

Infant (Aged ≥4 Weeks and Weighing ≥3 kg), Child, and Adolescent Dose

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 drugs that induce uridine diphosphate glucuronyl transferase (UGT) 1A or cytochrome P450 (CYP) 3A are coadministered, administer DTG dispersible tablets twice daily (see the Drug Interactions section below).

[Tivicay] DTG Film-Coated Tablets

Child and Adolescent (Weighing ≥14 kg) Dose

- 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 DTG 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 drugs that induce UGT1A or CYP3A are coadministered, administer DTG tablets twice daily (see the Drug Interactions section below).

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.

Adult Dose

- One 50-mg DTG film-coated tablet once daily
- If certain drugs that induce UGT1A or CYP3A are coadministered, administer DTG 50 mg twice daily (see the Drug Interactions section below).
- For DTG dispersible tablets, 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 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. DTG dispersible tablets should not be chewed or crushed.
- For ABC/DTG/3TC dispersible tablets, tablets should be fully dispersed in the appropriate volume of drinking water in the supplied cup and the suspension should be swirled 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 remains in the dosing cup. ABC/DTG/3TC dispersible tablets should not be swallowed whole, chewed, or crushed.
- No data exist regarding dispersion in breast milk or any vehicles other than water.
- In patients who have difficulty swallowing the film-coated 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 is reduced in patients with certain combinations of INSTI-resistance mutations. DTG dosing strategies in pediatric patients with first-generation INSTI mutations differ from those in adults (see Table A and the Resistance section below).
- Screen patients for hepatitis B virus (HBV) infection before using FDC tablets that contain 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.
- For any FDC tablets containing ABC, test patients for the HLA-B*5701 allele before starting therapy to predict the risk of HSRs. Patients who test positive for the HLA-B*5701 allele should not be given an ABC-containing FDC. Patients with no prior HLA-B*5701 testing who are tolerating an ABC- containing regimen do not need to be tested. See the Abacavir section.

- Adults who are INSTI-experienced with certain INSTI-associated resistance mutations or clinically suspected INSTI resistance should receive 50 mg DTG twice daily.

[Dovato] DTG/Lamivudine (3TC)

Adolescents Aged ≥12 Years and Weighing ≥25 kg and Adult Dose

- One tablet once daily with or without food as a complete regimen in antiretroviral (ARV)-naive adolescents with no known mutations associated with resistance to the individual components of Dovato

[Juluca] DTG/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 associated with resistance to the individual components of Juluca

[Triumeq PD] Abacavir (ABC)/DTG/3TC

Children Aged ≥3 Months and Weighing ≥6 kg to <25 kg

- Dispersible Triumeq PD tablets are FDA approved for children weighing ≥6 to <25 kg. They are not recommended for children weighing ≥25 kg.
- Administer the appropriate number of tablets for a child's weight once daily. Tablets should be dispersed in 15 mL of water if using three tablets or 20 mL of water if using four to six tablets, see Special Instructions. Triumeq PD tablets should not be swallowed whole, chewed, cut, or crushed.

Weight-Band Dosing of Triumeq PD Tablets for Children **Aged ≥3** Months and Weighing **≥6** kg

Weight	Recommended Daily Dose	Number of Triumeq PD Tablets
6 kg to <10 kg	ABC 180 mg, DTG 15 mg, 3TC 90 mg	3
10 kg to <14 kg	ABC 240 mg, DTG 20 mg, 3TC 120 mg	4
14 kg to <20 kg	ABC 300 mg, DTG 25 mg, 3TC 150 mg	5
20 kg to <25 kg	ABC 360 mg, DTG 30 mg, 3TC 180 mg	6
≥25 kg	Use Triumeq. See below.	

Metabolism/Elimination

- Substrate for UGT1A1 and CYP3A. Also, a substrate of UGT1A3, UGT1A9, breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp) *in vitro*. Drugs that induce these enzymes and transporters may decrease plasma concentrations of DTG. Drugs that inhibit these enzymes or transporters may increase DTG plasma concentrations.

DTG Dosing in Patients with Hepatic Impairment

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Due to the 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.

DTG 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-naive patients with mild, moderate, or severe renal impairment, or in INSTI-experienced patients with mild or moderate renal impairment.
- Use DTG with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance [CrCl] <30 mL/min), because DTG concentrations will be decreased. The cause of this decrease is unknown.
- FDC tablets containing 3TC (Dovato, Triumeq PD, and Triumeq) should not be used in patients who have CrCl <30 mL/min or patients who are on dialysis because the doses of 3TC cannot be adjusted. Data about the FDC DTG/3TC (Dovato) suggest that patients with a sustained creatinine clearance 30–49 mL/min may experience a higher 3TC exposure and should be monitored for hematologic toxicities and potential FDC discontinuation and subsequent adjustment of the treatment regimen. See package inserts for additional information.

• For use in patients who are ARV naive or ARV experienced (but INSTI naive) and who are not being treated with UGT1A1 or CYP3A inducers • See the Abacavir section for special instructions about testing for ABC hypersensitivity. [Triumeq] ABC/DTG/3TC *Child and Adolescent (Weighing ≥25 kg) and Adult Dose* • One tablet once daily with or without food • For use in patients who are ARV naive or ARV experienced (but INSTI naive) and who are not being treated with UGT1A1 or CYP3A inducers • See the Abacavir section for special instructions about testing for ABC hypersensitivity.	

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Dolutegravir (DTG) is a uridine diphosphate glucuronyl transferase (UGT) 1A and cytochrome P450 (CYP) 3A substrate and may require dose adjustments when administered with UGT1A-modulating or CYP3A-modulating medications. DTG dosing should be adjusted to twice daily (i.e., twice the usual dose) when coadministered with drugs such as efavirenz and rifampin.[2-4] 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. See the product label for a full listing of significant drug–drug interactions.
- Atazanavir (ATV) is an inhibitor of UGT1A1. In a 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.[5]
- 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 and increased body mass index (BMI) have been reported in adults who received DTG in clinical trials and in some pediatric and adolescent cohorts (see Table 17h. Lypodystrophies and Weight Gain).[6-9]
- *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 postmarketing reports note that neuropsychiatric adverse events (AEs) have occurred following the initiation of DTG-based therapy in adults.[10,11]

- *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 HIV disease and who initiated treatment with integrase strand transfer inhibitors (INSTIs), particularly DTG.[12,13] 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.[14,15]
- *Rare:* A single case of drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) has been reported.[16]

Resistance

The International Antiviral Society–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 is reduced in patients with the INSTI-resistance Q148 substitution plus two or more additional INSTI-resistance mutations, and this reduced efficacy cannot be completely overcome with increasing DTG dosing.[17,18]

For adults with first-generation INSTI-resistance mutations, the package insert recommends doubling the DTG dose and give the standard dose twice daily rather than once daily. However, modeling and simulation of this strategy with the dispersible tablet formulation of DTG in children suggested elevated maximum plasma concentrations (C_{max}) in comparison to historical data in adults, adolescents, and children would result. Thus, a different dosing strategy was needed for children with first-generation INSTI-resistance mutations. The proposed dosing schedule in Table A below was based on simulations with the goal of achieving geometric mean concentration at 12 hours postdose >1.97 µg/mL and area under the curve (AUC) through 12 hours postdose >32.2 µg·h/mL while avoiding elevated C_{max} values.[19] Additionally, the coformulated dispersible tablet containing abacavir (ABC)/DTG/lamivudine (3TC) cannot be used in combination with a separate dose of single-agent dispersible release DTG because the dosing of the separate formulation is not double the regular dose and the modified dosing strategy would result in underdosing the ABC and 3TC components.

Table A. Weight-Band Dosing of Dolutegravir Dispersible Tablets for Pediatric Patients Weighing ≥3 kg and Aged ≥3 Months with First-Generation INSTI-Resistance Mutations

Weight	Recommended Twice Daily Dose	Number of Tablets per Dose
3 kg to <6 kg	5 mg	1
6 kg to <10 kg	10 mg	2
10 kg to <14 kg	15 mg	3
14 kg to <20 kg	15 mg	3
20 kg to <30 kg	20 mg	4
30 kg to <40 kg	20 mg	4

Pediatric Use

Approval

DTG is approved by the FDA for use, in combination with other ARV drugs, in pediatric patients aged at least 4 weeks and weighing ≥3 kg who are treatment naive or treatment experienced but INSTI naive (see Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents). DTG dispersible tablets and film-coated tablets in either the single-entity or fixed-dose combination (FDC) form can be administered with or without food.[20,21] Pediatric patients weighing ≥20 kg may take the DTG 50-mg film-coated tablets if they are able to swallow tablets. The combination tablet ABC/DTG/3TC (Triumeq) is approved by the FDA for use in children and adolescents weighing ≥25 kg. Dispersible ABC/DTG/3TC tablets (Triumeq PD) are FDA approved for use in children weighing ≥10 kg to <25 kg. The combination tablet DTG/3TC (Dovato) is approved by the FDA for adolescents weighing ≥25 kg and aged ≥12 years but is not approved for use in children aged <12 years. The combination tablet DTG/rilpivirine (RPV) (Juluca) is not approved by the FDA for use in children or adolescents.

Formulation Differences: Film-Coated Tablet Compared to Dispersible Tablet

DTG is currently available as either film-coated tablets or dispersible tablets (tablets for oral suspension). The dispersible tablet has 60% to 80% greater bioavailability in adults than the film-coated tablet,[22] 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

Pediatric Patients Aged 4 Weeks to <18 Years

IMPAACT P1093 is an ongoing, multinational, open-label trial of DTG in children with HIV. Results of pharmacokinetic (PK), safety, and efficacy assessments have been reported sequentially for different age and weight cohorts as data became available; similarly, dosing recommendations have been revised sequentially.[23-25] Dosing recommendations that previously included the 25-mg film-coated tablets have been replaced with other formulations.

Data from IMPAACT 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 weighing ≥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 ranging in age from 1 month to 214 months received the currently approved dose (determined by weight and age) of DTG film-coated tablets or dispersible tablets. Eighty percent of participants were treatment experienced, but all were INSTI naive. 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 cell (CD4) count (percent) increase from baseline to Week 48 was 141 cells/mm^3 (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 participants.[26]

Sixteen adolescents in Cohort 1 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.[27]

A subsequent analysis of a larger group of 73 participants in Cohorts 3 through 5 (4 weeks to <6 years of age), who received the final proposed dose and of whom 87.7% were treatment experienced, confirmed safety as assessed to 48 weeks with no Grade 3 or higher AEs attributed to DTG. Of 68 participants with HIV RNA data at 48 weeks, 91% and 68% achieved HIV RNA <400 copies/mL and <50 copies/mL, respectively.[25]

The Once-daily DTG-based ART in Young people vS Standard thErapY (ODYSSEY) trial, conducted by the Pediatric European Network for the Treatment of AIDS (PENTA), enrolled both treatment-naive and treatment-experienced pediatric patients from the European Union, 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 707 children aged <18 years were enrolled; 311 children started DTG as first-line therapy, and 396 started DTG as second-line therapy.[28] As assessed by 96 weeks, DTG-based ART as both first-line therapy and second-line therapy in children was superior to standard care.[29] Results from the younger ODYSSEY cohort of children weighing between 3 and 14 kilograms showed superiority of DTG-based ART compared to other regimens, of which over 70% were protease inhibitor (PI)–based regimens.[29-31]

Nested PK substudies within ODYSSEY also evaluated simplified pediatric dosing that aligned with the World Health Organization's (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 DTG 30 mg administered as six 5-mg dispersible tablets. Both of these doses achieved AUC and maximum plasma concentration (C_{max}) values that were higher than adult PK reference values but still acceptable. Both doses achieved trough plasma concentration values that were slightly lower than adult reference values and exhibited greater variability but were determined to be acceptable.[32] Later-enrolling ODYSSEY cohorts included children weighing 3 kg to <20 kg.[33] Children weighing 14 kg to <20 kg received 25 mg and were enrolled first, then children weighing 3 kg to <6 kg and younger than 6 months received 5 mg DTG, 3 kg to <6 kg and older than 6 months received 10 mg, 6 kg to <10 kg received 15 mg, and 10 kg to <14 kg received 20 mg. For all weight bands, the DTG AUC through 24 hours post-dose was comparable to or higher than the target values in adults receiving the approved dose but within an acceptable safety margin. A total of 19 children weighing <20 kg experienced Grade 3 or higher AEs, including two deaths (one kwashiorkor and one accidental trauma) assessed as unrelated to the study drug. Eleven participants experienced serious AEs, 69% of which were due to infectious diseases. 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 B below. These data support the administration of either 30 mg as dispersible tablets or 50 mg as a 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 in infants at least 4 weeks of age and weighing at least 3 kg.

Separate PK studies have continued to support adequate DTG exposures among children and adolescents at the currently recommended doses.[20,34,35] Dosing in neonates is under investigation.

Table B: Summary of Pharmacokinetic Parameters in Pediatric Participants with HIV-1 (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[c]	DTG FCT 50 mg once daily		3.67 (20)	53.6 (27)	1,110 (46)
Adults[c]	DTG FCT 50 mg twice daily		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.[26]

Key: AUC_{0-24h} = 24-hour area under the curve; C_{24h} = concentration at 24 hours postdose; C_{max} = maximum plasma concentration; CV = coefficient of variation; DT = dispersible tablets; DTG = dolutegravir; FCT = film-coated tablets

Efficacy and safety of DTG-based regimens have been evaluated in multiple observational pediatric cohorts. Additional long-term efficacy and safety data for this age/weight group come from a retrospective, multicenter French cohort study that evaluated 134 children and adolescents who received DTG-based ART for at least 12 months. Most participants were ART experienced (90.3%) but integrase inhibitor naive (90.3%) and had virologic suppression at baseline (63.4%).[36] Virologic failure occurred in 43 participants (32%) and occurred more frequently when baseline viral load was ≥50 copies/mL (67.4% vs. 22.0%, $P < 0.01$). Resistance mutations to DTG emerged in one patient with virologic failure.[36] Retrospective analyses of children and adolescents aged ≤19 years and weighing ≥20 kg have also been performed from DTG rollout programs across Botswana, Eswatini, Lesotho, Malawi, Tanzania, and Uganda.[37] Of the 9,419 children and adolescents who initiated DTG between 2017 and 2020, 73% received tenofovir disoproxil fumarate (TDF)/3TC/DTG, 24% received ABC/DTG/3TC, and 3% received zidovudine/3TC/DTG. Only 0.7% reported a toxicity that resulted

in DTG discontinuation. Virologic suppression was documented in 92.7% (8,273 of 8,921) before switching to DTG. Following the switch, 93.4% (7,378 of 7,898) on DTG had documented virologic suppression, including 79.8% (426 of 534) of those not previously suppressed on their original regimen. However, the analysis did not include data for comparison among participants who were not suppressed and did not switch to a DTG-containing regimen. Factors associated with increased odds of virologic suppression included being virologically suppressed prior to ART switch (odds ratio [OR] 3.87; 95% confidence interval [CI], 3.03–4.95) and use of once-daily TDF/3TC/DTG as a single-tablet regimen (OR 1.78; 95% CI, 1.43–2.22), whereas age increases were associated with slightly reduced odds of virologic suppression (OR 0.94 for each 1-year increase; 95% CI, 0.91–0.97). A separate report among 3,347 children aged <14 years receiving DTG as part of a national rollout program in southern Mozambique revealed virologic suppression rates of 79.7% (63 of 79) in children newly initiating DTG and 85.8% (1,775 of 2,068) in those switching to DTG.[38] However, more than one-third experienced at least two regimen changes during the follow-up period from 2019 to 2021, some of which involved switching from DTG to either a PI or non-nucleoside reverse transcriptase inhibitor (NNRTI). These changes were attributable, in part, to drug shortage, illustrating the importance of continued access and supply of DTG to support rollout initiatives.

Although observational studies have shown high virologic suppression rates, emerging INSTI mutations specific to DTG have been reported among children being monitored in national treatment programs, as opposed to observational studies. Thus, continued assessments of virologic suppression longer term and the development of resistance will be important.[39,40]

The PK, safety, tolerability, and efficacy of dispersible and immediate-release FDC tablet formulations of ABC/DTG/3TC were investigated in children weighing 6 kg to <40 kg and aged <12 years among 57 children enrolled in the IMPAACT 2019 study.[41] Children were dosed across five weight bands in alignment with the WHO ARV dosing recommendations for each component. Children weighing 6 kg to <25 kg received the dispersible FDC formulation containing ABC 60 mg/DTG 5 mg/3TC 30 mg (Triumeq PD), and those weighing 25 to <40 kg received the immediate-release FDC formulation containing ABC 600 mg/DTG 50 mg/3TC 300 mg (Triumeq). Drug exposures for all three components were comparable to previous studies in children and adults with HIV, including DTG exposures from IMPAACT P1093 and ODYSSEY. Dosing was confirmed based on PK and safety criteria across all weight bands in alignment with WHO weight-band dosing recommendations. Data available through 24 weeks of treatment showed there were no Grade 3 or 4 AEs related to the drug components, and no participant discontinued the study drug because of AEs. At Week 24, 54 of 57 (95%) of participants were suppressed to <200 copies/mL, and all treatment-experienced patients who switched to ABC/DTG/3TC maintained suppression. Both formulations were also well tolerated, and 10 of 11 participants in the highest weight band were able to swallow the larger immediate-release tablet whole and intact (see Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents). Analyses of safety and efficacy data through 48 weeks are ongoing.

A separate cohort of adolescents in Barcelona, Spain, received the immediate-release FDC ABC 600 mg/DTG 50 mg/3TC 300 mg (Triumeq). Of the 12 patients described, 1 was treatment naive, 6 were undergoing treatment simplification, and 5 had previously experienced virologic failure on a different ART regimen. Nine of the 12 patients achieved or maintained viral suppression after switching to Triumeq; three patients did not 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, in contrast to tolerability findings in IMPAACT 2019.[42]

Pediatric Postmarketing Safety Studies

As long-term data are analyzed from the ODYSSEY trial, additional comparative safety information has been reported. The investigators reported a small number of neuropsychiatric AEs in the 707 children and adolescents randomized to DTG, not significantly different from those reported in study participants receiving standard care. However, participants receiving DTG were more likely to have suicidal ideation than those receiving standard care. Suicidal thoughts were reported by 13 participants receiving DTG, but none were reported among those receiving standard care; however, these symptoms were described as transient and did not lead to changes in ART.[30] A separate systematic review of INSTI use in children with perinatal HIV infection identified rates of neuropsychiatric effects from 1% to 16% among those receiving DTG (n=3,448 children).[43]

In a subset of ODYSSEY participants aged 6 to <18 years, no differences were identified in vitamin B12 levels across study arms, although plasma and RBC folate levels were lower among participants receiving standard care.[44]

Reports of weight gain among adults enrolled in clinical trials prompted similar studies to investigate metabolic effects of DTG in adolescents. A group of investigators in Eswatini analyzed BMI measurements retrospectively from a cohort of 460 virally suppressed adolescents switching to a DTG-based regimen (either ABC/DTG/3TC or TDF/3TC/DTG). In this cohort, both weight-for-age z-score and BMI-for-age z-score decreased slightly before transition to DTG but increased during the year after DTG was initiated. The rate of BMI increase per year was calculated to be about twofold greater than the normal rate in the full cohort, and about 2.8-fold greater among female adolescents.[7] A retrospective, single-center study of 97 children and adolescents who received a DTG-based regimen for at least 12 months in France showed that trajectories of BMI z-score change 12 months pre- versus 12 months post-DTG were similar, except in participants with baseline BMI ≥50th percentile, whose rate of BMI z-score change was lower post-DTG (difference: −0.23; $P = 0.04$).[45] Another group measured multiple body fat parameters and cholesterol/lipid profiles in Italian adolescents switched from a PI- or NNRTI-based regimen to a DTG-based regimen (ABC/DTG/3TC). Although BMI, body fat percentage, and limb fat percentage remained the same, trunk fat and trunk fat/total body fat ratio increased significantly. Total cholesterol and low density lipoproteins decreased, while serum triglycerides decreased early in the study and then increased by the end of the study.[6] A small, single-center cohort in Australia identified similar increases in BMI among adolescents switched to either DTG- or tenofovir alafenamide–containing regimens.[8] Another retrospective analysis of a cohort of children and adolescents in the District of Columbia who were initiated on INSTIs also identified a pattern of increasing BMI-for-age z-scores, with a mean rate of change of +0.19 z-score units per year.[9] The ODYSSEY investigators also assessed weight, height, and BMI over the course of their prospective, randomized study. At Week 96, they found that weight, height, and BMI-for-age z-score increased in children receiving DTG compared with those receiving standard care, with the adjusted difference in means of 1 kg, 0.8 cm, and 0.14 z-score units, respectively. The investigators noted that the differences between treatment groups were relatively small, emerged early, and stabilized within the 2-year study period.[31] A separate study in South Africa showed no significant change in BMI z-score, reduced hepatic steatosis, and lower total cholesterol and triglycerides among 30 adolescents switched to DTG in comparison to those who remained on their original ART regimen, the majority of which were PI-based (84%).[46] Another retrospective study in a Swiss cohort of 60 children with HIV did not identify any significant changes in BMI or BMI standard deviation scores associated with DTG when comparing at 1 year post-DTG switch.[47]

Based on these collective data, weight gain may be observed in adolescents receiving DTG, as observed in adults; the long-term clinical significance of these changes are unclear, and further studies are needed in adolescents and children receiving DTG. See the What to Start section for additional considerations.

Simplification of Treatment

Two trials in adults (Regimen Switch to Dolutegravir + Rilpivirine from Current Antiretroviral Regimen in Human Immunodeficiency Virus Type 1 Infected and Virologically Suppressed Adults [SWORD-1 and SWORD-2]) supported the approval of a DTG 50-mg/RPV 25-mg FDC tablet 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.[48] 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 INSTI-resistance was identified.[49] 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 TDF.[50]

The approval of DTG 50 mg/3TC 300 mg as a complete regimen was supported by data from two randomized, double-blind, controlled trials (Efficacy, Safety, and Tolerability Study Comparing Dolutegravir Plus Lamivudine With Dolutegravir Plus Tenofovir/Emtricitabine in Treatment naive HIV Infected Subjects [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 ≤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 who received DTG plus 3TC had a lower rate of adverse drug reactions (19.6%) than those who received DTG plus 3TC/TDF (25%).[51] The combination of DTG/3TC was evaluated as initial ART in adolescents weighing ≥25 kg and aged ≥12 years to <18 years with baseline HIV-1 RNA between 100 copies/mL and ≤500,000 copies/mL through the DANCE study. A total of 32 participants were enrolled, of which 81% and 69% achieved HIV RNA levels <50 copies/mL at Weeks 48 and 96, respectively.[52] These results included individuals with missing data due to site closures; thus, sensitivity analyses were performed with the participants excluded. Virologic suppression rates in the sensitivity analyses were 87% (26 of 30) at Week 48 and 88% (22 of 25) at Week 96. Drug exposures for both components were also comparable to historical data in adults and the combination was overall safe and well tolerated.

Although Juluca is not approved by the FDA for use in adolescents, the doses of the component drugs that make up this FDC tablet is approved for use in adolescents. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) usually endorses the use of adult formulations in adolescents, and these products may be appropriate for use in certain adolescents. The use of DTG/RPV regimens could be useful in patients in whom there is concern for

toxicity from nucleoside reverse transcriptase inhibitors. However, the Panel notes that adolescents may have difficulties adhering to therapy and suggests considering close monitoring with viral load testing (see the Treatment Simplification section of Management of Children Receiving Antiretroviral Therapy).

The combination of once-daily darunavir/ritonavir (DRV/r) with an INSTI is being investigated in a randomized non-inferiority trial among virologically suppressed children aged 6 years to <18 years through the SMILE Penta-17-ANRS 152 clinical trial.[53] Participants were randomized to either once-daily DRV/r with an INSTI or continuing their standard-of-care regimen consisting of a boosted PI or NNRTI with a nucleoside reverse transcriptase inhibitor backbone. A total of 318 participants were enrolled between 2016 and 2019, of which 158 were randomized to DRV/r with an INSTI (97% DTG, 3% elvitegravir). DRV/r with an INSTI was non-inferior to standard of care at Week 48 (HIV viral load ≥50 copies/mL in 5% for DRV/r with an INSTI vs. 7.6% in the standard-of-care arm; difference −2.5% [95% CI, −7.6% and 2.5%]). Secondary analyses comparing DRV/r with an INSTI versus standard of care revealed decreases in CD4 counts (−48.3 cells/mm^3 [95% CI, −93.4 and −3.2; $P = 0.036$] and mean high-density lipoprotein change from baseline (−4.1 mg/dL [95% CI, −6.7 and −1.4; $P = 0.003$]), and increases in weight and BMI (+1.97 kg [95% CI, 1.1 and 2.9; $P < 0.001$] and +0.66 kg/m^2 [95% CI, 0.3 and 1.0; $P < 0.001$], respectively). A nested PK substudy in 153 adolescents aged ≥12 years to <18 years from SMILE also demonstrated that total and unbound DTG concentrations were adequate and well above the protein-adjusted 90% inhibitory concentration for DTG.[54] DTG trough concentrations were also comparable to those measured in adults receiving 50 mg once daily. Apparent clearance of the unbound drug was influenced by total bilirubin concentrations and Asian ethnicity.

Crushing Film-Coated Tablets for Administration

Dispersible tablets are now considered the preferred formulation for pediatric patients weighing <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 must be consumed **immediately.**[1] In healthy adults, the use of crushed tablets resulted in slightly higher exposures than the use of whole tablets.[55] 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 tube[56] or nasogastric tube.[57] 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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