Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Dolutegravir (DTG, Tivicay)  (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: https://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Tablets: 10 mg, 25 mg, and 50 mg

Fixed-Dose Combination Tablets:
- [Juluca] Dolutegravir 50 mg/rilpivirine 25 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg

Dosing Recommendations

Neonate and Infant Dose:
- Dolutegravir is not approved for use in neonates/infants.

Child and Adolescent Dose:
- No dosing recommendations can be made for children weighing <25 kg.
- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends an investigational dose of dolutegravir 50 mg once daily for children and adolescents weighing ≥25 kg who are antiretroviral (ARV)-naive or ARV-experienced (but integrase strand transfer inhibitor [INSTI]-naive) and who are not being treated with uridine diphosphate glucuronyl transferase (UGT) 1A1 or cytochrome P450 3A (CYP3A) inducers.
- The Panel’s recommended dose is based on interim data from ongoing trials that indicate that using the FDA-approved dose of dolutegravir 35 mg in patients weighing ≥30 kg to 40 kg may result in suboptimal trough concentrations (see text). Using a 50-mg dose also avoids the need to administer two tablets with different strengths (i.e., a 10-mg tablet plus a 25-mg tablet). Dolutegravir is not approved by the Food and Drug Administration (FDA) for use in children weighing <30 kg.

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) have been reported.

Special Instructions

- Dolutegravir may be taken without regard to meals.
- Dolutegravir 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.
- In patients who have difficulty swallowing tablets whole, 10-mg, 25-mg, and 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 dolutegravir 50 mg twice daily is reduced in patients with certain combinations of INSTI-resistance mutations (see the Resistance section below).
- When using fixed-dose combination (FDC) tablets that contain dolutegravir, see other sections of the Drug Appendix for special instructions and additional information about the individual components of the FDC.
Metabolism/Elimination

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

Dolutegravir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Due to a lack of data, dolutegravir is not recommended for use in patients with severe hepatic impairment.
- Dolutegravir decreases tubular secretion of creatinine and increases measured serum creatinine, without affecting glomerular filtration.

Dolutegravir Dosing in Patients with Renal Impairment:

- 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 dolutegravir with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance <30 mL/min), because dolutegravir concentrations will be decreased. The cause of this decrease is unknown.

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

- Metabolism: Dolutegravir is a uridine diphosphate glucuronyl transferase (UGT) 1A1 and cytochrome P450 3A (CYP3A) substrate and may require dose adjustments when administered with UGT1A-modulating or CYP3A-modulating medications. Because etravirine significantly reduces plasma concentrations of dolutegravir, dolutegravir should not be administered with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir, which counteract this
effect on dolutegravir concentrations. Dolutegravir should not be administered with nevirapine because of insufficient data on interactions between these drugs.

- Atazanavir is an inhibitor of UGT1A1. In a recent pharmacologic survey of adult patients who were receiving dolutegravir, patients who also received atazanavir had plasma concentrations of dolutegravir that were two-fold to four-fold higher than those of patients who received other antiretroviral (ARV) drugs.2
- Before administering dolutegravir, clinicians should carefully review a patient’s medication profile for potential drug interactions.

**Major Toxicities**

- *More common:* Insomnia and headache.
- *Less common (more severe):* Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction. Neuropsychiatric symptoms, especially in patients with a history of psychiatric illness. Multiple post-marketing reports note neuropsychiatric adverse effects (AEs) following initiation of dolutegravir-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 inhibitors, particularly dolutegravir.5,6 This phenomenon is presumed to be linked to the rapid decline in HIV RNA observed in patients receiving integrase inhibitor therapy.
- *Rare:* Hepatotoxicity has been reported; two cases of liver injury were presumed to be related to the use of dolutegravir. 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, an increased number of neural tube defects was observed among infants born to women who were receiving dolutegravir at the time of conception.10,11 Further data collection is ongoing, and additional analyses from this study and from other investigations will be required to confirm this potential safety signal. Before patients become sexually active, pediatric and adolescent providers should discuss this potential risk of neural tube defects with patients who are receiving or initiating dolutegravir and their caregivers. Specific recommendations about the initiation and use of dolutegravir in women of childbearing potential and in pregnant women are available in the Adult and Adolescent Antiretroviral Guidelines (see Table 6b and Adolescents and Young Adults with HIV) and in the Perinatal Guidelines (see Teratogenicity and Recommendations for Use of Antiretroviral Drugs During Pregnancy).

**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 dolutegravir 50 mg twice daily is reduced in patients with the integrase strand transfer inhibitor (INSTI)-resistance Q148 substitution plus two or more additional INSTI-resistance mutations.

**Pediatric Use**

**Approval**

Dolutegravir is approved by the Food and Drug Administration (FDA) for use in combination with other ARV drugs in children and adolescents weighing ≥30 kg who are treatment-naive or treatment-experienced but INSTI-naive at dolutegravir doses that are lower than the adult dose, although the Panel suggests it can be used in children and adolescents weighing ≥25 kg, see Appendix A, Table 2.12 The World Health Organization (WHO), however, recommends using dolutegravir at the adult dose of 50 mg
in children weighing ≥25 kg. This recommendation is based on pharmacokinetic (PK) and safety data from two ongoing clinical trials (IMPAACT P1093 and ODYSSEY) that are described below. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) agrees with the WHO assessment of these data. The combination tablet abacavir/dolutegravir/lamivudine (Triumeq) is approved for use in children and adolescents weighing ≥40 kg, although the Panel suggests it can be used in children and adolescents weighing ≥25 kg (see Appendix A, Table 2). The combination tablet dolutegravir/rilpivirine (Juluca) is not approved for use in children or adolescents at the time of this review.

Efficacy and Pharmacokinetics

Children and Adolescents Aged ≥12 Years and Weighing ≥40 kg

IMPAACT P1093 is an ongoing open-label trial of dolutegravir in children with HIV. Initial FDA approval of dolutegravir for use in adolescents weighing ≥40 kg was based on data from 23 treatment-experienced, INSTI-naive adolescents. Intensive PK evaluations were performed on the first 10 participants, nine of whom weighed ≥40 kg and received dolutegravir 50 mg and one of whom weighed 37 kg and received dolutegravir 35 mg. These doses resulted in exposures comparable to those seen in adults receiving 50 mg once daily. Nine of 10 participants achieved HIV RNA concentrations <400 copies/mL at Week 4 (optimal background therapy was added 5 days–10 days after dolutegravir was started). An additional 13 participants were then enrolled for evaluation of long-term outcomes. At 48 weeks, 61% of participants had achieved HIV RNA concentrations <50 copies/mL. No safety or tolerability concerns were identified. By Week 144, 39% and 30% of participants had achieved HIV RNA concentrations <400 copies/mL and <50 copies/mL, respectively. All participants who experienced virologic failure were nonadherent.

Additional long-term safety and efficacy data for this age/weight group comes from a French, retrospective, multicenter cohort study that evaluated 50 adolescents who initiated dolutegravir-based ART. Of 17 adolescents who were virologically suppressed at the time of dolutegravir-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 dolutegravir, 19 (58%) achieved sustained virologic success. Overall, 66% of patients achieved sustained virologic suppression and 78% had undetectable plasma viral load by the last study visit. Adolescents with virologic failure were more likely to be from sub-Saharan Africa and had more frequently detectable viremia in the 6 months prior to dolutegravir initiation. No resistance mutations emerged in patients with virologic failure, and only one patient discontinued dolutegravir-based treatment because of a significant AE (dizziness and sleep disturbance).

Another cohort of adolescents in Barcelona received the fixed-dose combination (FDC) product abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg (Triumeq). Of the twelve patients reported, 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 due to suboptimal adherence. Of note, patients complained about the size of the tablet and six reported having to crush or split the tablet in order to swallow it (see Appendix A, Table 2).

Children and Adolescents Aged <12 Years

The ODYSSEY trial, conducted by the Pediatric European Network for the Treatment of AIDS (PENTA) is enrolling 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 (EMA; see below). A total of 674 children aged <18 years were enrolled; 282 children started dolutegravir as first-line therapy and 392 started dolutegravir as second-line therapy. Nested PK substudies within ODYSSEY are also evaluating simplified pediatric dosing that aligns with WHO-recommended weight bands. PK data are available from a cohort of children weighing ≥25 kg who switched to the 50-mg dolutegravir tablet (N = 27). Children weighing ≥25 kg who received the 50-mg, film-coated tablet achieved exposures similar to those seen in adults who received the same dose. When given to children weighing 14 kg to <25 kg, the dolutegravir 25-mg, film-coated tablet resulted in drug exposures that were lower than the target exposure for adults, particularly C_{\text{trough}}. The median C_{\text{trough}} was lower in the 20 kg
to <25 kg group than in the 14 kg to <20 kg group. Higher doses are currently under study in these weight bands, and doses for lower weight bands in the study have been adjusted accordingly.20,21

In addition, a younger cohort of children aged ≥6 years to <12 years had PK assessment and remains in longer-term follow up in IMPAACT P1093, with those weighing ≥30 kg to <40 kg receiving the 35 mg dose and those weighing ≥40 kg receiving the 50 mg dose. At 48 weeks, data from 23 participants demonstrated a favorable safety profile, adequate PKs, and virologic efficacy, with HIV RNA concentrations of <50 copies/mL achieved in 17 of 23 participants (74%).16,22 These data led to the FDA approval of the lower-strength, film-coated dolutegravir tablets at a dose of 35 mg for use in children with HIV who weigh ≥30 kg to <40 kg. The FDA did not approve dosing for children weighing <30 kg because the available PK data in lower weight bands were minimal and the observed C_{trough} concentrations were lower than expected.

The EMA used the same data to inform population PK modelling and simulation analyses to approve the lower-strength, film-coated dolutegravir tablets for use in children aged ≥6 years and weighing ≥15 kg.23 The EMA approved doses of dolutegravir 20 mg for children weighing 15 kg to <20 kg and doses of 25 mg for those weighing 20 kg to <30 kg. As noted above, evaluation of these doses during the ODYSSEY study indicated that many children failed to achieve adequate trough concentrations. The Panel agrees with the WHO dosing recommendation of dolutegravir 50 mg (as the film-coated tablet) for pediatric patients weighing ≥25 kg and does not recommend use of dolutegravir in children weighing <25 kg. Further data are needed to determine an appropriate dose for this weight group.

The safety and effectiveness of the EMA dosing strategy was evaluated in a cohort of children aged 6 years to <18 years in the United Kingdom and Ireland who were followed during the CHIPS study. Between January 2014 and March 2018, 174 children in the cohort received dolutegravir at the EU-licensed doses. Of these 174 children, 53% were female, 91% had perinatally acquired HIV, and the median age was 15.5 years at the initiation of dolutegravir (interquartile range: 13.5 years–16.7 years). Only 6% of the cohort was treatment-naïve, and 38% had previous exposure to three classes of ARVs. Overall, nine participants (5%) discontinued dolutegravir; three discontinued because of toxicity, three because an alternative regimen was available, and three for other reasons or missing reasons. Viral suppression was reported in 80 of 95 participants (84%) who remained on dolutegravir for 6 months, and viral suppression was reported in 41 of 49 participants (84%) who remained on dolutegravir for 12 months. Median changes in CD4 T lymphocyte cell counts were -9 cells/mm³ at 6 months (N = 81) and -47 cells/mm³ at 12 months (N = 41) of dolutegravir treatment.24

**Children Aged <6 Years Who Are Not Able to Swallow Tablets**

IMPAACT P1093 also investigated the use of solid, oral-dosage forms of dolutegravir in patients aged as young as 4 weeks. Among the initial doses studied, a dolutegravir granule formulation was well tolerated; area under the curve (AUC₂₄₉ₙ) values were within target ranges, but C₂₄₉ₙ levels were below target ranges.25 In response to stakeholder feedback, the manufacturer decided to stop development of the granules and instead developed a dispersible tablet formulation. The dispersible tablet has 60% to 80% greater bioavailability in adults than the film-coated tablet,26 so doses studied using the dispersible tablet cannot be directly compared to those using the film-coated tablet. The first presentation of the data on dolutegravir dispersible tablets reported that three age cohorts of 10 patients (≥4 weeks to <6 months, ≥6 months to <2 years, and ≥2 years to <6 years) received protocol-defined, weight-based dosing using combinations of 5-mg, dispersible tablets. While target AUC₂₄₉ₙ and C₂₄₉ₙ levels were achieved in the youngest cohort, C₂₄₉ₙ levels were low in children 6 months to <6 years of age. The dispersible tablet formulation was well-tolerated by all age groups. Higher doses are being evaluated in some age/weight groups.27

**Simplification of Treatment**

Two trials in adults (SWORD-1 and SWORD-2) supported the approval of a dolutegravir 50 mg/rilpivirine 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 patients with suppressed viral replication 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 to either receive dolutegravir/rilpivirine or to continue...
their suppressive ARV regimen. After 48 weeks of treatment, 95% of patients in both arms maintained HIV RNA <50 copies/mL. More AEs were reported and led to discontinuation in the dolutegravir/rilpivirine arm. In a subgroup of SWORD study patients whose original ARV regimen contained tenofovir disoproxil fumarate, small but statistically significant increases in hip and spine bone mineral density were observed. Although Juluca is not approved for use in adolescents, Juluca contains doses of dolutegravir and rilpivirine that are approved for use in adolescents as drugs. The Panel usually endorses the use of adult formulations in adolescents, and this product 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 Juluca in adolescents and children until more data are available.

**Crushing Film-Coated Tablets for Administration**

In patients who have difficulty swallowing whole tablets, 50-mg tablets (and 10-mg or 25-mg tablets, should they need to be used) 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. 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.

**References**

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