

## Dolutegravir (Tivicay, Tivicay PD, DTG)

Updated: January 31, 2023

Reviewed: January 31, 2023

### Summary

- No dose adjustment for dolutegravir (DTG) is recommended in pregnancy.
- First-trimester exposure to DTG has not been associated with increased risk of congenital anomalies, including neural tube defects (NTDs).

### Human Studies in Pregnancy

#### Pharmacokinetics

DTG pharmacokinetics (PK) in human pregnancy have been reported in three studies and a series of case reports.<sup>1-7</sup> In a safety and PK study of 29 pregnant women in the United States, DTG plasma concentrations were lower during pregnancy than postpartum, with DTG area under the curve (AUC) reduced by 21% during pregnancy. Although trough concentrations ( $C_{\text{trough}}$ ) were reduced by 34% during the third trimester compared to postpartum,  $C_{\text{trough}}$  during pregnancy were well above 0.064  $\mu\text{g/mL}$ , the 90% effective concentration for DTG. DTG was well tolerated by these pregnant women. During the third trimester, HIV-1 RNA was below 50 copies/mL in 27 of 29 participants, and no infants acquired HIV.<sup>5</sup> Similar reductions in DTG exposure were seen in a study of 15 European pregnant women, with DTG AUC reduced by 14% and minimum concentration ( $C_{\text{min}}$ ) by 26% during pregnancy compared to postpartum. DTG was well tolerated, and all participants had viral load below 50 copies/mL during the third trimester.<sup>7</sup>

In contrast, PK sampling during pregnancy and the early postpartum period of 17 African women who were receiving DTG showed a small reduction in DTG maximum concentration ( $C_{\text{max}}$ ) and no differences in the 24-hour concentration and AUC from 0 to 24 hours when geometric mean ratios in pregnancy were compared to the postpartum period. However, postpartum sampling was performed at a median of 10 days postpartum, when maternal physiology had not yet fully returned to the nonpregnant state.<sup>6</sup> In the case reports, DTG was used safely and effectively in individual pregnant women and plasma exposures were adequate.<sup>1-4</sup>

#### Placental and Breast Milk Passage

Placental transfer of DTG in an *ex vivo* perfusion model was high, with a mean fetal-to-maternal concentration ratio of 0.6.<sup>8</sup> In two *in vivo* PK studies,<sup>5,6</sup> the median DTG cord blood-to-maternal plasma concentration ratios were 1.21 and 1.25. High placental transfer of DTG has also been reported in several of the case reports.<sup>1,3,4</sup> In 17 breastfeeding mothers, the median ratio of DTG in breast milk to maternal plasma was 0.03. Their infants had a median DTG  $C_{\text{max}}$  of 66.7 ng/mL (range 21–654 ng/mL) and a median  $C_{\text{min}}$  of 60.9 ng/mL (range 16.3–479 ng/mL) at a median age of 10 days (range 7–18 days). The geometric mean ratio of infant plasma-to-maternal plasma DTG concentrations in these 17 mother-infant pairs was 0.03.<sup>6</sup>

## Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to DTG to detect at least a twofold increase in the risk of overall birth defects. No such increase in the risk of birth defects has been observed with DTG. Among the cases of first-trimester DTG exposure that had been reported to the Antiretroviral Pregnancy Registry as of January 31, 2021, the prevalence of birth defects was 3.2% (22 of 696 live births; 95% confidence interval, 2.0–4.8).<sup>9</sup> Supplemental data from the Antiretroviral Pregnancy Registry on central nervous system (CNS) birth defect outcomes in 1,131 live births to women who were exposed to DTG during periconception or pregnancy reported 5 infants with CNS birth defects: 2 of 571 infants with periconception exposure, 1 of 125 infants with exposure late in the first trimester, and 2 of 434 infants with second- or third-trimester exposure. One of the CNS defects was an NTD in an infant with periconception exposure; no encephalocele defects were reported.<sup>9</sup>

In the U.S. PK study in pregnant women discussed above, birth abnormalities were reported in 7 of 29 infants: 3 with normal variants; 1 with total anomalous pulmonary venous return (DTG was initiated at 16 weeks gestation); 1 with a polycystic right kidney (DTG was initiated at 11 weeks gestation); 1 with an isolated left renal cyst (DTG was initiated at 12 weeks gestation); and 1 with jitteriness and chin tremors (DTG was initiated at 28 weeks gestation).<sup>5</sup> DTG was initiated at 28 weeks gestation or later in the PK study in African women discussed above, and no congenital anomalies were observed among 28 live births.<sup>6</sup> In reviews of clinical experience with pregnant women who received DTG, birth defects were noted in 4 infants born to 81 European women, in 2 infants born to 66 women from the United States, and in no infants born to 116 women from Botswana who received DTG during the first trimester.<sup>10-12</sup> No increased incidence of birth defects or adverse perinatal outcomes was observed in 57 French women receiving DTG during pregnancy compared to matched controls who did not receive integrase strand transfer inhibitors (INSTIs) during pregnancy.<sup>13</sup>

In July 2019, a report from a National Institutes of Health–funded surveillance study of birth outcomes among pregnant women in Botswana who were receiving antiretroviral therapy found that DTG exposure at the time of conception was associated with a slightly higher rate of NTDs than other types of antiretroviral (ARV) drug exposure (0.30% vs. 0.10%).<sup>14</sup> Expanded and ongoing surveillance of birth outcomes in Botswana among pregnant women receiving ARVs between August 2014 and March 2022, revealed a prevalence of NTDs with DTG use at conception of 0.11%, which was identical to the NTD prevalence in women with HIV receiving other ARVs at conception.<sup>15</sup>

INSTI regimens, including those with DTG, in both nonpregnant and pregnant adults living with HIV are associated with more weight gain than regimens without INSTIs.<sup>16,17</sup> In high-resource countries where undernutrition is less common, the increase in gestational weight gain associated with use of DTG has the potential to lead to more adverse pregnancy outcomes, such as gestational hypertension, gestational diabetes mellitus, and macrosomia.<sup>18</sup> In low-resource countries where undernutrition is common, the increase in gestational weight gain associated with DTG use may reduce the number of women at risk for certain severe adverse pregnancy outcomes associated with low maternal weight, as well as increase the number at risk of adverse pregnancy outcomes associated with high maternal weight.<sup>16</sup>

## ***Animal Studies***

### **Carcinogenicity**

DTG has not been shown to be genotoxic or mutagenic *in vitro*. No carcinogenicity was detected in 2-year, long-term studies in mice at DTG exposures that were up to 14-fold higher than the exposures achieved in humans with systemic exposure to the recommended dose. In addition, no carcinogenicity was detected in rats at DTG exposures up to 10-fold higher in males and 15-fold higher in females than the exposures seen in humans who received the recommended dose.<sup>19</sup>

### **Reproduction/Fertility**

DTG did not affect fertility in male and female rats and rabbits at doses that produced exposures (based on AUC) that were approximately 27-fold higher than that achieved in humans who received the recommended dose.<sup>19</sup>

### **Teratogenicity/Adverse Pregnancy Outcomes**

Studies of DTG in rats and rabbits have shown no evidence of developmental toxicity, teratogenicity, or effects on reproductive function.<sup>19</sup>

### **Placental and Breast Milk Passage**

Studies in rats have demonstrated that DTG crosses the placenta and is excreted into breast milk.<sup>19</sup>

**Excerpt from [Table 14](#)**

**Note:** When using fixed-dose combination (FDC) tablets, refer to other sections in [Appendix B](#) and [Table 14](#) in the Perinatal Guidelines for information about the dosing and safety of individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations <sup>a</sup>	Use in Pregnancy
<p><b>Dolutegravir</b> (DTG) <i>Tivicay</i> <i>Tivicay PD</i></p> <p>(DTG/3TC) <i>Dovato</i></p> <p>(DTG/RPV) <i>Juluca</i></p> <p>(DTG/ABC/3TC) <i>Triumeq</i></p>	<p><b>DTG (Tivicay)</b></p> <ul style="list-style-type: none"> <li>DTG 10-mg, 25-mg, and 50-mg film-coated tablets</li> </ul> <p><b>DTG (Tivicay PD)</b></p> <ul style="list-style-type: none"> <li>DTG 5-mg dispersible tablet for oral suspension</li> </ul> <p><b>DTG film-coated tablets and DTG dispersible tablets are not bioequivalent and are not interchangeable.</b></p> <p><b>DTG/3TC (Dovato)</b></p> <ul style="list-style-type: none"> <li>DTG 50-mg/3TC 300-mg tablet</li> </ul> <p><b>DTG/RPV (Juluca)</b></p> <ul style="list-style-type: none"> <li>DTG 50-mg/RPV 25-mg tablet</li> </ul> <p><b>DTG/ABC/3TC (Triumeq)</b></p> <ul style="list-style-type: none"> <li>DTG 50-mg/ABC 600-mg/3TC 300-mg tablet</li> </ul>	<p><b>Pregnancy</b></p> <p><i>PKs in Pregnancy</i></p> <ul style="list-style-type: none"> <li>AUC may be decreased during the third trimester compared with postpartum, but exposures during pregnancy are well above those needed to inhibit viral replication.</li> </ul> <p><i>Dosing in Pregnancy</i></p> <ul style="list-style-type: none"> <li>No change in dose indicated.</li> </ul> <p>For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., <a href="#">ABC</a>, <a href="#">3TC</a>, <a href="#">RPV</a>).</p> <p><b>Standard Adult Doses</b></p> <p><i>In ARV-Naive or ARV-Experienced (but INSTI-Naive) Patients</i></p> <ul style="list-style-type: none"> <li>DTG (Tivicay) <ul style="list-style-type: none"> <li>One 50-mg tablet once daily, without regard to food</li> </ul> </li> <li>DTG (Tivicay PD) <ul style="list-style-type: none"> <li>Six 5-mg tablets (30 mg) dissolved in water once daily, without regard to food</li> </ul> </li> <li>DTG/3TC (Dovato) <ul style="list-style-type: none"> <li>One tablet once daily, without regard to food</li> </ul> </li> <li>DTG/RPV (Juluca) <ul style="list-style-type: none"> <li>One tablet once daily, with food</li> </ul> </li> </ul>	<p>High placental transfer to fetus<sup>b</sup></p> <p>No evidence of teratogenicity in rats or rabbits. The most recent data from Botswana indicates the prevalence of NTDs in infants born to pregnant women with HIV receiving DTG at conception is no longer statistically different than in those receiving other antiretrovirals.</p> <p>DTG is a <i>Preferred</i> antiretroviral drug for use during pregnancy, irrespective of trimester, and for people who are trying to conceive (see <a href="#">Recommendations for Use of Antiretroviral Drugs During Pregnancy</a> and <a href="#">Table 5</a>).</p> <p>To maximize DTG absorption, doses should not be administered within 2 hours of ingesting any preparation that contains such minerals as iron or calcium, including prenatal vitamins.</p>

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations <sup>a</sup>	Use in Pregnancy
		<ul style="list-style-type: none"> <li>• DTG/ABC/3TC (Triumeq) <ul style="list-style-type: none"> <li>○ One tablet once daily, without regard to food</li> </ul> </li>   <li><i>In ARV-Naive or ARV-Experienced (but INSTI-Naive) Patients Who Are Also Receiving EFV, FPV/r, TPV/r, or Rifampin</i></li> <li>• DTG (Tivicay) <ul style="list-style-type: none"> <li>○ One 50-mg tablet twice daily, without regard to food</li> </ul> </li> <li>• DTG (Tivicay PD) <ul style="list-style-type: none"> <li>○ Six 5-mg tablets (30 mg) dissolved in water twice daily, without regard to food</li> </ul> </li>   <li><i>In INSTI-Experienced Patients</i></li> <li>• DTG (Tivicay) <ul style="list-style-type: none"> <li>○ One tablet twice daily, without regard to food</li> </ul> </li> </ul>	

<sup>a</sup> Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency. For details, see the [Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 11](#).

<sup>b</sup> Placental transfer categories are determined by mean or median cord blood-to-maternal delivery plasma drug ratio:

**High:** >0.6  
**Moderate:** 0.3–0.6  
**Low:** <0.3

**Key:** 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; AUC = area under the curve; DTG = dolutegravir; EFV = efavirenz; FPV/r = fosamprenavir/ritonavir; INSTI = integrase strand transfer inhibitor; NTD = neural tube defect; PK = pharmacokinetic; RPV = rilpivirine; TPV/r = tipranavir/ritonavir

## References

1. Pain JB, Le MP, Caseris M, et al. Pharmacokinetics of dolutegravir in a premature neonate after HIV treatment intensification during pregnancy. *Antimicrob Agents Chemother.* 2015;59(6):3660-3662. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25845873>.
2. Pinnetti C, Tintoni M, Ammassari A, et al. Successful prevention of HIV mother-to-child transmission with dolutegravir-based combination antiretroviral therapy in a vertically infected pregnant woman with multiclass highly drug-resistant HIV-1. *AIDS.* 2015;29(18):2534-2537. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26372490>.
3. Lewis JM, Railton E, Riordan A, Khoo S, Chavonda M. Early experience of dolutegravir pharmacokinetics in pregnancy: high maternal levels and significant foetal exposure with twice-daily dosing. *AIDS.* 2016;30(8):1313-1315. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27128333>.
4. Schalkwijk S, Feiterna-Sperling C, Wezsacker K, et al. Substantially lowered dolutegravir exposure in a treatment-experienced perinatally HIV-1-infected pregnant woman. *AIDS.* 2016;30(12):1999-2001. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27428578>.
5. Mulligan N, Best BM, Wang J, et al. Dolutegravir pharmacokinetics in pregnant and postpartum women living with HIV. *AIDS.* 2018;32(6):729-737. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29369162>.
6. Waitt C, Orrell C, Walimbwa S, et al. Safety and pharmacokinetics of dolutegravir in pregnant mothers with HIV infection and their neonates: a randomised trial (DOLPHIN-1 study). *PLoS Med.* 2019;16(9):e1002895. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31539371>.
7. Bollen P, Freriksen J, Konopnicki D, et al. The effect of pregnancy on the pharmacokinetics of total and unbound dolutegravir and its main metabolite in women living with human immunodeficiency virus. *Clin Infect Dis.* 2021;72(1):121-127. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32103260>.
8. Schalkwijk S, Greupink R, Colbers AP, et al. Placental transfer of the HIV integrase inhibitor dolutegravir in an ex vivo human cotyledon perfusion model. *J Antimicrob Chemother.* 2016;71(2):480-483. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26538508>.
9. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 January 2022. Wilmington, NC: Registry Coordinating Center; 2022. Available at: [http://www.apregistry.com/forms/interim\\_report.pdf](http://www.apregistry.com/forms/interim_report.pdf).
10. Thorne C, Favarato G, Peters H, et al. Pregnancy and neonatal outcomes following prenatal exposure to dolutegravir. Presented at: International AIDS Society Conference, 2017. Paris, France. Available at: [https://www.natap.org/2017/IAS/IAS\\_133.htm](https://www.natap.org/2017/IAS/IAS_133.htm)
11. Zash R, Jacobson DL, Diseko M, et al. Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an

- observational study. *Lancet Glob Health*. 2018;6(7):e804-e810. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29880310>.
12. Grayhack C, Sheth A, Kirby O, et al. Evaluating outcomes of mother-infant pairs using dolutegravir for HIV treatment during pregnancy. *AIDS*. 2018;32(14):2017-2021. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29944472>.
  13. Sibiude J, Le Chenadec J, Mandelbrot L, et al. Risk of birth defects and perinatal outcomes in HIV-infected women exposed to integrase strand inhibitors during pregnancy. *AIDS*. 2021;35(2):219-226. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33048878>.
  14. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. *N Engl J Med*. 2019;381(9):827-840. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31329379>.
  15. Zash R, Holmes L.B., Diseko M., Jacobson D., et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo Study, Botswana. Presented at: AIDS 2022; 2022. Montreal, Canada. Available at: <https://programme.aids2022.org/Abstract/Abstract/?abstractid=12759>.
  16. Zash R, Caniglia EC, Diseko M, et al. Maternal weight and birth outcomes among women on antiretroviral treatment from conception in a birth surveillance study in Botswana. *J Int AIDS Soc*. 2021;24(6):e25763. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34176240>.
  17. Eckard AR, McComsey GA. Weight gain and integrase inhibitors. *Curr Opin Infect Dis*. 2020;33(1):10-19. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31789693>.
  18. Asif S, Baxevanidi E, Hill A, et al. The predicted risk of adverse pregnancy outcomes as a result of treatment-associated obesity in a hypothetical population receiving tenofovir alafenamide/emtricitabine/dolutegravir, tenofovir disoproxil fumarate/emtricitabine/dolutegravir or tenofovir disoproxil fumarate/emtricitabine/efavirenz. *AIDS*. 2021;35(Suppl 2):S117-S125. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34261099>.
  19. Dolutegravir (tivicay and tivicaay PD) [package insert]. Food and Drug Administration. 2021. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/204790s028,213983s0021b1.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204790s028,213983s0021b1.pdf).