Dolutegravir (Tivicay, Tivicay PD, DTG)

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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.[1-7] In a safety and PK study of 29 pregnant women in the United States, total 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_{trough}) were reduced by 34% during the third trimester compared to postpartum, C_{trough} during pregnancy were well above 0.064 µg/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.[5] A subsequent analysis revealed that DTG protein binding in these women was decreased during pregnancy so that unbound DTG concentrations during late pregnancy were comparable to postpartum concentrations, despite the decrease in total (bound plus unbound) concentrations.[8] 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_{min}) by 26% during pregnancy compared to postpartum. DTG was well tolerated, and all participants had viral loads below 50 copies/mL during the third trimester.[7]

In contrast, PK sampling during pregnancy and the early postpartum period of 17 African women receiving DTG showed a small reduction in DTG maximum concentration (C_{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.[6] In the case reports, DTG was used safely and effectively in individual pregnant women and plasma exposures were adequate.[1-4]

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.[9] In two *in vivo* PK studies,[5,6] 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.[1,3,4] 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_{max} of 66.7 ng/mL (range 21–654 ng/mL) and a median C_{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.[6]

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for DTG and other antiretroviral (ARV) drugs twice a year through an interim report released in June and December. The APR has monitored sufficient numbers of first-trimester exposures to DTG to detect at least a 1.5-fold increase in the risk of overall birth defects and at least a twofold increase in the risk of cardiovascular and genitourinary defects (which are the more common classes of birth defects in the general population). No such increase in the risk of birth defects has been observed with DTG. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to DTG and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals. The data in Figure 1 can be compared with the prevalence in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP] and with the Texas Birth Defects Registry ([TBDR] 5.07 per 100 live births).

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).[5] 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.[6] 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.[10-12] 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.[13] In contrast, in 257 pregnancies in women with HIV in Denver, Colorado, diverse congenital anomalies (with no NTDs) were detected in 7 of 24 infants (29.2%) exposed to DTG in the first trimester compared to 13 of 109 infants (11.9%) with first-trimester exposure to non-INSTI ARVs.[14]

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 ARV drug exposure (0.30% vs. 0.10%).[15] 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.[16] In a report from an ongoing birth outcome surveillance program in Eswatini, NTD prevalence was 0.08% in 4,832 pregnancies with DTG use at conception compared to 0.16% in 1,248 pregnancies with use of non-DTG regimens at conception and 0.08% in 17,270 pregnancies without HIV infection.[17] When the data from the Botswana and Eswatini programs are combined, the NTD prevalence is 0.098% in more than 14,000 women receiving DTG at conception, which is not significantly different from the NTD rates in women receiving other ARV regimens at conception or women without HIV in these countries.[18]

INSTI regimens, including those with DTG, are associated with weight gain and other metabolic effects, such as hyperglycemia and changes in folate metabolism, both during pregnancy and among nonpregnant adults with HIV.[19,20] The impact of these metabolic effects on pregnancy outcomes is unknown.[20] 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 associated with high maternal weight, such as gestational hypertension, gestational diabetes mellitus, and macrosomia.[21] 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.[22] In a study randomizing pregnant women from nine countries (88% from sub-Saharan Africa) to DTG- or efavirenz-based ARV regimens, women receiving DTG had greater antepartum weight gain, which was associated with fewer adverse pregnancy outcomes.[23] Additional research is critically needed to describe the impact of the metabolic effects of DTG on pregnancy outcomes.

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.[24]

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.[24]

Teratogenicity/Adverse Pregnancy Outcomes

Studies of DTG in rats and rabbits have shown no evidence of developmental toxicity, teratogenicity, or effects on reproductive function.[24]

Placental and Breast Milk Passage

Studies in rats have demonstrated that DTG crosses the placenta and is excreted into breast milk.[24]

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**[a]	**Use in Pregnancy**
Dolutegravir (DTG) *Tivicay* *Tivicay PD* (DTG/3TC) *Dovato* (DTG/RPV) *Juluca* (DTG/ABC/3TC) *Triumeq*	**DTG (Tivicay)** • DTG 10-mg, 25-mg, and 50-mg film-coated tablets **DTG (Tivicay PD)** • DTG 5-mg dispersible tablet for oral suspension **DTG film-coated tablets and DTG dispersible tablets are not bioequivalent and are not interchangeable.** **DTG/3TC (Dovato)** • DTG 50-mg/3TC 300-mg tablet **DTG/RPV (Juluca)** • DTG 50-mg/RPV 25-mg tablet **DTG/ABC/3TC (Triumeq)** • DTG 50-mg/ ABC 600-mg/ 3TC 300-mg tablet	**Pregnancy** *PK in Pregnancy* • AUC may be decreased during the third trimester compared with postpartum, but exposures during pregnancy are well above those needed to inhibit viral replication. *Dosing in Pregnancy* • No change in dose indicated. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., ABC, 3TC, RPV). **Standard Adult Doses** *In ARV-Naive or ARV-Experienced (but INSTI-Naive) Patients* • DTG (Tivicay) o One 50-mg tablet once daily, without regard to food • DTG (Tivicay PD) o Six 5-mg tablets (30 mg) dissolved in water once daily, without regard to food • DTG/3TC (Dovato) o One tablet once daily, without regard to food • DTG/RPV (Juluca) o One tablet once daily, with food	High placental transfer to fetus[b] No evidence of teratogenicity in rats or rabbits. The most recent data from Botswana indicate 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 ARVs. DTG is a *Preferred* ARV drug for use during pregnancy, irrespective of trimester, and when trying to conceive (see Recommendations for Use of Antiretroviral Drugs During Pregnancy and Table 7). 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. **Note:** Please see FDA label for full list of drugs with potential interactions and drugs for which administration with

Excerpt From Table 14

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
		• DTG/ABC/3TC (Triumeq) o One tablet once daily, without regard to food *In ARV-Naive or ARV-Experienced (but INSTI-Naive) Patients Who Are Also Receiving EFV, FPV/r, TPV/r, or Rifampin* • DTG (Tivicay) o One 50-mg tablet twice daily, without regard to food • DTG (Tivicay PD) o Six 5-mg tablets (30 mg) dissolved in water twice daily, without regard to food *In INSTI-Experienced Patients* • DTG (Tivicay) o One tablet twice daily, without regard to food	DTG is contraindicated.

[a] 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.

[b] 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

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