



**Recommendations for the Use of Antiretroviral Drugs in
Pregnant Women with HIV Infection and Interventions to Reduce
Perinatal HIV Transmission in the United States**

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Dolutegravir (Tivicay, DTG)

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The Antiretroviral Pregnancy Registry does not contain enough reports regarding exposure to dolutegravir during pregnancy to develop a drug-associated risk determination for birth defects and miscarriage. A preliminary report from observational surveillance of birth outcomes among pregnant women on antiretroviral therapy (ART) in Botswana found an increased number of neural tube defects (NTDs) among infants born to women who were on a dolutegravir-based regimen initiated prior to pregnancy that they were receiving at time of conception. There was no significant increase in the risk of NTDs among infants born to women who initiated dolutegravir during pregnancy.

Animal Studies

Carcinogenicity

Dolutegravir was not genotoxic or mutagenic *in vitro*. No carcinogenicity was detected in 2-year, long-term studies in mice at dolutegravir 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 dolutegravir 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.¹

Reproduction/Fertility

Dolutegravir did not affect fertility in male and female rats and rabbits at doses that produced systemic area under the curve (AUC) approximately 27-fold higher than that achieved in humans who received the recommended dose.¹

Teratogenicity/Adverse Pregnancy Outcomes

Studies of dolutegravir in rats and rabbits have shown no evidence of developmental toxicity, teratogenicity, or effects on reproductive function.¹

Placental and Breast Milk Passage

Studies in rats have demonstrated that dolutegravir crosses the placenta and is excreted into breast milk.¹

Human Studies in Pregnancy

Pharmacokinetics

Dolutegravir pharmacokinetics (PK) in human pregnancy have been reported in **three** studies and a series of case reports.²⁻⁸ In a safety and PK study of **29** pregnant women in the United States, dolutegravir plasma concentrations were lower during pregnancy than postpartum, **with dolutegravir AUC reduced by 21% during pregnancy. Although trough concentrations were reduced by 34% during the third trimester compared to postpartum, trough concentrations in pregnancy were well above 0.064 µg/mL, the 90% effective concentration for dolutegravir. Dolutegravir 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.**⁷ In **two smaller** studies of five pregnant women from Europe **and seven from Africa**, dolutegravir was well tolerated and the reduction in plasma exposures during pregnancy was **similar to the one observed in the study described above.**^{6,8} In the case reports, dolutegravir was used safely and effectively in **individual pregnant women** and plasma exposures were adequate.²⁻⁵

Placental and Breast Milk Passage

Placental transfer of dolutegravir in an *ex vivo* perfusion model was high, with a fetal-to-maternal ratio of 60%.⁹ **In the largest *in vivo* PK study, median cord blood-to-maternal ratio for dolutegravir concentration was 1.25 and high placental transfer of dolutegravir has been reported** in several of the case reports.^{2,4,5,7} In one breastfeeding mother who was receiving dolutegravir, the dolutegravir breast milk-to-maternal-plasma-concentration ratio was **0.2** and the dolutegravir concentration in **breast milk and in infant plasma** was 0.10

mg/L, equal to the dolutegravir target trough plasma concentration in treatment-naive patients.¹⁰

Teratogenicity/Adverse Pregnancy Outcomes

Among live births reported to the Antiretroviral Pregnancy Registry as of **January 31, 2018**, the overall birth defect rate for infants with **first-trimester** exposure to dolutegravir was **3.1%** (**five** infants out of **161** live births).¹¹ In the largest PK study in pregnant women discussed above, birth abnormalities were reported in **seven of 29** infants: **three with normal variants; one with** total anomalous pulmonary venous return (**dolutegravir was initiated at 16 weeks' gestation**); **one with a** polycystic right kidney (**dolutegravir was initiated at 11 weeks' gestation**); **one with an isolated left renal cyst** (**dolutegravir was initiated at 12 weeks' gestation**); and **one with jitteriness and chin tremors** (**dolutegravir was initiated at 28 weeks' gestation**).⁷ In two reviews of clinical experience with pregnant women who received dolutegravir, birth defects were noted in **four** infants born to **81** European women, **in two infants born to 66 women from the United States**, and in no infants born to 116 women from Botswana who received dolutegravir during the first trimester.¹²⁻¹⁴

A preliminary report from a National Institutes of Health-funded observational surveillance study of birth outcomes among pregnant women on ART in Botswana indicated a potential increase in the incidence of NTDs among infants born to women who initiated a dolutegravir-based regimen prior to pregnancy that they were receiving at the time of conception.^{13,15} **The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission conservatively recommends that dolutegravir not be initiated during the first trimester of pregnancy (<14 weeks [up to 13 6/7 weeks] gestational age by last menstrual period) or in women who are trying to conceive (see Interim Recommendations about the Use of Dolutegravir in Pregnancy in Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Teratogenicity).**

Excerpt from Table 10^a

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Dolutegravir (DTG) <i>Tivicay</i> (DTG/RPV) <i>Juluca</i> (DTG/ABC/3TC) <i>Triumeq</i>	DTG (Tivicay) <i>Tablet:</i> <ul style="list-style-type: none"> DTG 50 mg tablet 	<u>Standard Adult Doses</u> <i>In ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive) Patients</i> <i>DTG (Tivicay):</i> <ul style="list-style-type: none"> 1 tablet once daily, without regard to food 	High placental transfer to fetus. ^b No evidence of teratogenicity in mice, rats, or rabbits. Preliminary data suggest a possible increased risk of NTDs in infants born to women who initiated DTG prior to pregnancy and were receiving it at the time of conception. Dolutegravir <u>should not be initiated</u> during the first trimester of pregnancy (less than 14 weeks [up to 13 6/7 weeks] gestational age by LMP.) For more information see Interim Guidance about the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy . To maximize DTG absorption, doses should not be administered within 2 hours of ingestion of any preparation containing minerals such as iron or calcium, including prenatal vitamins.
	DTG/RPV (Juluca): <ul style="list-style-type: none"> DTG 50 mg plus RPV 25 mg tablet 	<i>DTG/RPV (Juluca):</i> <ul style="list-style-type: none"> 1 tablet once daily with food 	
	DTG/ABC/3TC (Triumeq): <ul style="list-style-type: none"> DTG 50 mg plus ABC 600 mg plus 3TC 300 mg tablet 	<ul style="list-style-type: none"> 1 tablet once daily, without regard to food <i>ARV-Naive or ARV-Experienced (but Integrase Inhibitor-Naive) if Given with EFV, FPV/r, TPV/r, or Rifampin; or Integrase Inhibitor-Experienced</i> <i>DTG (Tivicay):</i> <ul style="list-style-type: none"> 1 tablet twice daily, without regard to food <u>PK in Pregnancy:</u> <ul style="list-style-type: none"> AUC may be decreased during the third trimester compared with postpartum, but good viral suppression observed in third-trimester recipients. <u>Dosing in Pregnancy:</u> <ul style="list-style-type: none"> No change in dose indicated. For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., ABC, 3TC, RPV) 	

^a Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the [Adult and Adolescent Guidelines, Appendix B, Table 8](#)).

^b Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

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

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; AUC = area under the curve; DTG = dolutegravir; EFV = efavirenz; **FDC = fixed-dose combination**; FPV/r = fosamprenavir/ritonavir; **LMP = last menstrual period**; **NTD = neural tube defect**; PK = pharmacokinetic; **RPV = rilpivirine**; TPV/r = tipranavir/ritonavir

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