Safety Data on *Dovato* during Pregnancy

Summary

- There are currently limited human data on the use of *Dovato* (dolutegravir/lamivudine [DTG/3TC]).[1]
  - Further monitoring of DTG pre-natal exposure and maternal/fetal outcomes is required.
- In the PREGNANCY pilot study, 20 pregnant women with HIV naïve to antiretroviral therapy (ART) were started on DTG/3TC at a gestational age between 14 and 28 weeks.[2] All women achieved an undetectable viral load, no therapy modifications were necessary during the study, and no adverse events were related to the ART. No cases of perinatal HIV transmission were detected
- In the August 2022 analysis from the Tsepamo study, there were 12 neural tube defects (NTDs) out of 11,110 pregnancies exposed to DTG at conception (prevalence 0.11%) with no statistically significant difference compared to non-DTG ART exposures.[3,4]
- Healthcare providers are encouraged to report all antiretroviral-exposed pregnancies to the Antiretroviral Pregnancy Registry (APR) prospectively (http://www.apregistry.com).
- Important safety information and boxed warning(s) can be found in the Prescribing Information link and can also be accessed at Our HIV Medicines.

To access additional scientific information related to ViiV Healthcare medicines, visit the ViiV US Medical Portal at viivhcmedinfo.com.

OVERVIEW OF RISK DURING PREGNANCY

There are limited human data on the use of DTG/3TC during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage.[1]

Data from the Antiretroviral Pregnancy Registry has not demonstrated an increased risk of overall birth defects with DTG or 3TC compared with population-based surveillance systems.[1,5]

Preliminary 2018 findings from the Tsepamo birth outcomes surveillance study in Botswana reported a higher than expected number of NTDs among newborns whose mothers were exposed to DTG-based ART at the time of conception.[6,7] Over time, the prevalence of NTDs has decreased as the number of pregnancies with DTG exposure have increased.[8] As of the most recent report in August 2022, there was no longer evidence for a statistically significant difference in NTD occurrence between DTG and non-DTG ARV exposure at conception (total of 12 NTDs out of 11,110 pregnancies exposed to DTG, corresponding to a prevalence of 0.11% and a prevalence difference vs non-DTG ART exposures from conception of -0.02% [95% CI, -0.09% to 0.05%]).[3,4]

In addition, data from a hospital birth surveillance study in Eswatini indicated similar rates of NTDs regardless of DTG exposure or maternal HIV status.[9] For further background information on the risk of NTDs with DTG-based regimens, click here.

TREATMENT GUIDELINES

The Department of Health and Human Services (DHHS) Panel includes a DTG-based regimen as one of the recommended options for persons of childbearing potential initiating ART.[10] Before initiating a DTG-based

regimen, clinicians should discuss the risks and benefits of using DTG with persons of childbearing potential to allow an informed decision to be made. In the Perinatal Guidelines, the Panel recommends DTG as a preferred initial ARV during pregnancy.[11] 3TC (as part of a dual-NRTI backbone) is also included as a preferred initial ARV.

DTG/3TC (and other 2-drug regimens) is not recommended by DHHS as an initial regimen during pregnancy due to insufficient data.[11] Women who present to care on DTG/3TC and have maintained viral suppression can continue the 2-drug regimen with more frequent viral load monitoring (every 1-2 months) throughout pregnancy.

The World Health Organization (WHO) Consolidated Guidelines recommend DTG in combination with an NRTI backbone as the preferred first-line regimen in adults and adolescents.[12] The potential signal of NTDs for women of childbearing potential was examined and because of the lower than initially observed risk, its use for women of childbearing potential is not affected.

The European AIDS Clinical Society (EACS) Guidelines include DTG in combination with 2 NRTIs as a preferred, recommended regimen for ART-naïve pregnant women.[13] DTG/3TC is not included as a recommended or alternative regimen. The decision of switching ART for women planning to or becoming pregnant while already on ART should be individualized.

DATA FROM CLINICAL STUDIES OF DTG/3TC

Female participants were not eligible to enroll in the GEMINI-1 and -2, TANGO, SALSA, or STAT studies if they were pregnant (as confirmed by a pregnancy test at screening) or lactating.[14-18] Females of childbearing potential agreed to protocol-defined contraception to avoid pregnancy. Participants who became pregnant during a study, changed their mind and desired to become pregnant, or were no longer willing to comply with approved pregnancy avoidance methods were required to be withdrawn from the study.

A total of 12 pregnancies have been reported from the DTG/3TC clinical development program.[14-18] Six pregnancies occurred during the GEMINI-1 and -2 studies, 1 pregnancy during the STAT study, 2 during the TANGO study, and 3 during the SALSA study. No apparent congenital anomalies were reported. Outcomes are provided in Table 1.

Table 1. Pregnancy Outcomes for Clinical Study Participants Exposed to DTG/3TC[a,14-18]

Study	Participant Age (Years)[b]	Week of Gestation	Duration of Exposure (Days)	Outcome
GEMINI-1	20-30	39	513	Live Birth
GEMINI-1	30-40	7	425	Spontaneous Abortion
GEMINI-1	20-30	NR	1036	NR
GEMINI-2	20-30	6	111	Induced Abortion
GEMINI-2	20-30	6	1008	Elective Abortion
GEMINI-2	20-30	5	848	Elective Abortion
TANGO	40	27	92	Premature Labor (Live Birth)
TANGO	28	NA	987	Ongoing
SALSA	40-50	7[c]	40 (from conception)	Spontaneous Abortion
SALSA	30-40	5[d]	37 (from conception)	Elective Termination
SALSA	20-30	Unknown	Unknown	Presumed Abortion (either spontaneous or elective)
STAT	24	38	176	Live Birth

[a] DTG and 3TC were administered as separate components in the GEMINI studies; [b] Age at screening; [c] Reported as 7 weeks and 4 days; [d] Reported as 5 weeks and 2 days.
3TC = lamivudine; DTG = dolutegravir; NA = not applicable; NR = not reported.

PREGNANCY PILOT STUDY

PREGNANCY was a single-arm, single center, pilot study conducted in Brazil.[2] The study enrolled 20 pregnant women between January 2019 and March 2021 who were living with HIV, naïve to ART with viral load of at least 1000 copies/mL, at least 15 years old, and had a gestational age between 14 and 28 weeks. Participants were excluded if they had genotypic resistance mutations to DTG or 3TC, active hepatitis B or C, anemia, the presence of congenital abnormality on ultrasound, or use of interacting concomitant medications. Once enrolled, participants were started on fixed-dosed combination DTG/3TC. The primary outcome was the proportion of women and infants who had an undetectable viral load (HIV-1 RNA < 50 copies/mL) at the time of delivery.

At baseline, the mean age was 25.4 ± 5.4 years, mean gestational age of 18 ± 4.0 weeks, the median CD4 cell count was 401.6 ± 113.6 cells/μL, and the median viral load was 9514 copies/mL (range 1049 – 118455).[2] The mean gestational age at delivery was 38.8 ± 1.0 weeks.

All women achieved an undetectable viral load after receiving DTG/3TC an average of 40.4 ± 23.7 days.[2] No therapy modifications were necessary during the study, and no adverse events were related to the ART.

No cases of perinatal HIV transmission were detected.[2] Fourteen (70%) of the infants were delivered through cesarean delivery, as this was reported as the preferred delivery method by the women in the study (1 cesarean delivery had an obstetric indication of arterial hypertension). Infants had an average weight of 3158 g and length of 48 cm. The mean Apgar score was 8.6 and 9.4 at 1 and 5 minutes, respectively, after birth. Infants were not breastfed, and they received oral zidovudine for 28 days.

NONCLINICAL DATA

Upon administering DTG, no adverse effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed up to the highest dose tested (1000 mg/kg/day).[1] No evidence of fetal malformations due to 3TC was observed in rats and rabbits at doses producing plasma concentrations approximately 35 times higher than human exposure at the recommended human dose.

PREGNANCY EXPOSURE REGISTRY

To monitor maternal-fetal outcomes of pregnant women, an Antiretroviral Pregnancy Registry (APR) has been established (http://www.apregistry.com). This is a voluntary prospective, exposure-registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to antiretroviral products. Healthcare providers are encouraged to report all antiretroviral-exposed pregnancies to the APR prospectively.

This information is scientific and non-promotional in nature and is not intended for further distribution.

This information is not intended to offer recommendations for using this product in a manner inconsistent with its approved labeling. Please consult the Prescribing Information. For ViiV Healthcare to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 877-844-8872.

Selection of references follows principles of evidence-based medicine and, therefore, references may not be all inclusive.

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