Maternal and Infant Outcomes of Dolutegravir-Based Regimens Used During Pregnancy

Summary

- There are no adequate and well-controlled studies evaluating the use of dolutegravir-based regimens (DBRs) in pregnant women. Pregnancy was an exclusion criterion in all phase 3 trials evaluating the efficacy and safety of DBRs as a 3-drug regimen.[1-8]
- The Department of Health and Human Services (DHHS), European AIDS Clinical Society (EACS), and World Health Organization (WHO) all list DTG as a part of a 3-drug regimen as a preferred ARV in pregnancy.[9-11]
- Through January 16, 2019, there were a total of 1060 pregnancies reported among women receiving single-entity dolutegravir (DTG) or abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) recorded in the ViiV Healthcare global safety database (includes voluntary reporting, post-marketing studies, and ViiV Healthcare-sponsored clinical trials).[12] See Table 1 below for details.
- In the March 2022 analysis from the Tsepamo study, there was no longer a significant difference in NTDs with the use of DTG-containing compared to non-DTG containing ARV regimens at conception.[13] For additional details, click here.
- Maternal safety and pregnancy outcomes from other cohorts and case series are presented below.
- Important safety information can be found in the Prescribing Information links for *Tivicay* and *Triumeq* (including a boxed warning for *Triumeq*) and can 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.

PREGNANCY GUIDELINE RECOMMENDATIONS

The DHHS, EACS, and WHO guidelines recommend DTG in combination with a dual-nucleoside reverse transcriptase inhibitor (NRTI) backbone as a preferred ART for pregnant people who are treatment-naïve, who have received ARV drugs in the past and who are restarting ART, the current regimen is not well tolerated and/or is not fully suppressive, nonpregnant people who are trying to conceive, and continuing ART for people who become pregnant on a fully suppressive, well-tolerated regimen.[9-11] For information on guideline recommendations on DTG/3TC, click here. DTG should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.[14] Women of childbearing potential who are taking DTG-based regimens should be counselled about the potential risk of NTDs with DTG, including consideration of effective contraceptive measures.

CLINICAL STUDIES AND POST-MARKETING SURVEILLANCE

There are no adequate and well-controlled studies evaluating the use of dolutegravir-based regimens (DBRs) in pregnant women. Pregnancy was an exclusion criterion in all phase 3 trials evaluating the efficacy and safety of DBRs.[1-8] Investigational product was to be discontinued as soon as possible upon detection of pregnancy. Dolutegravir was given at a dose of 50 mg once daily. For details on maternal and infant outcomes with DTG/3TC, click here.

Through 16 January 2019, there were 757 pregnancy outcomes with DTG exposure and 303 with ABC/DTG/3TC for a total of 1060 pregnancies with exposure to DTG-containing products.[12] See Table 1 for pregnancy outcomes reported.

Table 1. Cumulative Pregnancy Outcomes Reported After Maternal Exposure[a][12]

Outcome	DTG Exposure	ABC/DTG/3TC Exposure	Total
ViiV-sponsored studies			
Live infant, no apparent congenital anomaly	24	9	33
Live infant, congenital anomaly	1	0	1
Spontaneous abortion, no apparent congenital anomaly	11	3	14
Ectopic pregnancy	2	0	2
Elective termination, no apparent congenital anomaly	15	4	19
Pregnancy Ongoing	5	2	7
Pregnancy outcome unknown/lost to follow-up	3	1	4
Total	61	19	80
Post-marketing surveillance[b]			
Live infant, no apparent congenital anomaly[c]	240	74	314
Live infant, congenital anomaly	89	24	113
Spontaneous abortion, congenital anomaly	3	8	11
Stillbirth, congenital anomaly	1	1	2
Elective termination, congenital anomaly	2	5	7
Spontaneous abortion, no apparent congenital anomaly	51	18	69
Stillbirth, no apparent congenital anomaly	34	0	34
Ectopic pregnancy	2	2	4
Elective termination, no apparent congenital anomaly	22	4	26
Pregnancy Ongoing	108	59	167
Pregnancy outcome unknown/lost to follow-up	144	89	233
Total	696	284	980

[a] Data cutoff January 16, 2019; [b] Includes published data from the Tsepamo study up to July 2018; [c] Includes outcomes where it is unknown whether a congenital anomaly occurred

3TC = lamivudine; ABC = abacavir; DTG = dolutegravir

Through 16 January 2019, a total of 134 congenital abnormalities were identified in patients exposed to dolutegravir during pregnancy.[12] Ninety-six were exposed to DTG given as a single entity and 38 were exposed to ABC/DTG/3TC. Forty-three of the congenital abnormalities were identified as umbilical hernia and the majority of the rest of the remaining congenital abnormalities were related to the nervous system (n=14), cardiac system (n=13), and musculoskeletal system (n=8). One hundred and sixteen cases of congenital abnormalities provided information on the trimester of exposure to either DTG or ABC/DTG/3TC:

- 1st trimester: 49 cases (including 33 cases exposed at conception)
- 2nd trimester: 20 cases
- 3rd trimester: 47 cases

There were 9 confirmed cases of NTDs with mothers exposed to DTG or ABC/DTG/3TC: 6 from Tsepamo study (as of March 2019) and 3 spontaneous cases as of 31 January 2019 (1 from Nambia reported in January 2017 and 2 from the United States, both reported in June 2018).[12]

CLINICAL DATA FROM DTG-BASED 3-DRUG REGIMENS

Meta-Analysis

A meta-analysis was performed to collect data from randomized controlled trials that measured pregnancy outcomes with DTG use.[15] A review of clinicaltrials.gov identified 5 randomized-controlled trials that compared DTG + 2 nucleoside reverse transcriptase inhibitors (NRTIs) vs previous standard of care EFV + 2 NRTIs in 1074 pregnant women. The primary endpoints included viral suppression, the number of stillbirths, neonatal deaths and HIV-mother-to-child-transmissions (MTCTs).

Table 2. Meta-analysis Included Randomized Controlled Trials[15]

Trial	Location	Treatment Arms	Sample Size (pregnant women)	
			DTG-Arm	EFV-arm
DolPHIN-1 (enrolled in 3rd trimester)	South Africa, Uganda	TDF/XTC + DTG vs TDF/XTC/EFV	29	31
DolPHIN-2 (enrolled in 3rd trimester)	South Africa, Uganda	TDF/XTC + DTG vs TDF/XTC/EFV	137	131
NAMSAL (from conception)	Cameroon	TDF/3TC + DTG vs TDF/3TC/EFV	13	12
ADVANCE (from conception)	South Africa	TAF/FTC + DTG vs TDF/FTC + DTG vs TDF/FTC/EFV	26 25	30
IMPAACT 2010 (Enrolled in 2nd/3rd trimester)	Brazil, Botswana, India, Tanzania, Thailand, South Africa, USA, Zimbabwe	TAF/FTC + DTG vs TDF/FTC + DTG vs TDF/FTC/EFV	216 213	211

DTG = dolutegravir; EFV = efavirenz; FTC = emtricitabine; 3TC = lamivudine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; XTC = patients could have received lamivudine or emtricitabine

DTG was associated with significantly higher levels of viral suppression compared to EFV with an OR: 2.90, 95% CI: 1.54, 5.46, $P = 0.01$.[15] Viral suppression was defined as HIV-1 RNA < 50 copies/mL in ADVANCE, DolPHIN-1, and DolPHIN-2; HIV-1 RNA < 200 copies/mL in IMPAACT 2010; and NAMSAL did not have viral suppression results for pregnant women. The viral load was measured at delivery in each trial.

There were 5/659 cases of MTCT in the DTG-arm and 0/415 cases of MTCT in the EFV-arm.[15]

Table 2. Adverse Birth Outcomes Among Births[15]

Outcome	DTG-arm % (n/N)	EFV-arm % (n/N)	*P* value
MTCT	5 (5/659)	0 (0/415)	0.18
Preterm birth	8 (52/633)	12 (47/392)	0.04
SGA	17 (80/467)	18 (45/251)	0.38
≥ 1 AE experienced by Mothers	22 (141/649)	18 (73/403)	0.73
≥ 1 AE experienced by Infants	22 (130/590)	28 (105/370)	0.06
Stillbirth	4 (26/659)	2 (9/415	0.06
Neonatal death	2 (10/659	3(12/415)	0.68

AE = adverse event; DTG = dolutegravir; EFV = efavirenz; MTCT = mother to child transmission; SGA = small for gestational age

Table 3. Overview of Clinical Data on DTG-based 3DRs in Pregnancy (≥ 5 pregnancies exposed to DTG)

Study	Study Analysis	Country	Pregnancies exposed to DTG	Outcomes
DolPHIN-1[16]	Open-label, Phase 3, randomized trial in women with untreated HIV by at least 28 weeks gestation	Uganda and South Africa	29 (all participants initially started on an EFV-based regimen)	• 69% in the DTG-arm had an undetectable HIV-1 RNA VL vs 39% in the EFV- arm (*P*=0.02)[a] • One stillbirth was reported in the DTG arm • Two participants in the DTG-arm experienced ≥ 1 Grade 3 AE; none were reported in the EFV-arm. The specific Grade 3 AEs were not reported. • Two participants in the DTG-arm experienced ≥ SAE. These included 1 case of decreased Hgb (not related), malaria (possibly related), UTI (possibly related), stillbirth (not related), ALT & Bili increased (possibly related), hypokalemia (possibly related), and hyponatremia (possibly related)
DolPHIN-2[17]	Open-label, Phase 3, randomized trial in women at least 28 weeks pregnant	Uganda and South Africa	135	• HIV-1 RNA <50 copies/mL at birth: 89/120 (74.2%) in the DTG-arm and 50/117 (42.7%) in the EFV-arm • Median time to achieve VL < 50 copies/mL was 28 days (95% CI 28-34) in the DTG-arm and 82 days (95% CI 55-97) in the EFV-arm • 3 MTCTs all in the DTG-arm believed to have occurred in utero • 3 stillbirths in the DTG-arm (all considered unrelated to treatment) • 19% of participants experienced a SAE in the DTG-arm (n=137) vs 13.7% in the EFV arm (n=131); 1.5% of participants experienced ≥1 drug-related AE in the DTG-arm compared to 3.8% in the EFV-arm
IMPAACT 2010[18]	Open-label, Phase 3, randomized trial for pregnant women	International	432	• 395 (98%) in the combined DTG groups had delivery HIV-1 RNA <200 copies/mL vs 182 (91%) in the EFV group (difference 7% [95% CI 2%, 11%]; *P*=0·005) • 8/216 stillbirths in the DTG+FTC/TAF arm & 11/213 in the DTG+FTC/TDF arm • 33/202 SGA in the DTG+FTC/TAF arm & 45/200 in the DTG+FTC/TDF arm • 12/208 preterm births in the DTG+FTC/TAF arm & 19/202 in the DTG+FTC/TDF arm • Estimated risk of MTCT ranged from 0.5-1% across the arms: DTG + FTC/TAF 0.98%, DTG + FTC/TDF 0.5%, and EFV/FTC/TDF 0.55% • Rates of maternal & infant Grade ≥3 AEs were similar across study arms from enrollment to Week 50 postpartum
IMPAACT P1026[19]	Open-label, Phase 4, nonrandomized trial	US	29	• 4 infants were preterm (<37 weeks gestation), 5 were SGA, and 4 were low birth weight (<2500 grams) • Congenital abnormalities in 7/29 infants; 2 were considered possibly related to DTG exposure (renal abnormalities)
ADVANCE[20]	Open-label, Phase 3, randomized trial	South Africa	54	• Birth outcomes: 7 spontaneous abortions in the DTG + TAF/FTC arm; 14 elective abortions (7 in each DTG arms); no stillbirths; 1 neonatal death in the DTG+TAF/FTC arm • No HIV vertical transmissions and no NTDs reported

[a] Among patients tested between postpartum days 0-14

AE = adverse event; ALT = alanine aminotransferase; CI = confidence interval; DTG = dolutegravir; EFV = efavirenz; FTC = emtricitabine; MTCT = mother to child transmission; NTDs = neural tube defects; SAE = serious AE; SGA = small for gestational age; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; UTI = urinary tract infection; VL = viral load

POST-MARKETING REPORTS AND OBSERVATION COHORTS

Antiretroviral Pregnancy Registry

Data are available from cases prospectively reported to the APR through 31 January 2022.[21] The rate of birth defects in infants born to mothers receiving an integrase strand transfer inhibitor-based regimen can be found in Table 4 below.

Table 4. Prevalence of Birth Defects in Infants Born to Mothers Receiving an Integrase Strand Transfer Inhibitor-Based Regimen During Pregnancy[21]

INSTI	1st Trimester Exposure Defects/Live Births (Prevalence, 95% CI)[a]	2nd/3rd Trimester Exposure % (n/N, 95% CI)[a]
Dolutegravir	22/696 (3.2%, 2.0-4.7)	21/434 (4.8%, 3.0-7.3)
Cabotegravir	1/3	0/0
Bictegravir	5/183	0/51
Elvitegravir	11/396 (2.8%, 1.4-4.9)	1/70 (1.7%, 0.0-7.7)
Raltegravir	18/537 (3.4%, 2.0-5.2)	16/450 (3.6%, 2.0-5.7)

[a] Prevalence and 95% confidence intervals are reported for drugs with a denominator of ≥ 200 first trimester exposed live births

CI=confidence interval

Following the initial reports of NTDs from Botswana an additional analysis was conducted to assess the relationship of integrase strand transfer inhibitor exposure and the development of birth defects among infants born to mothers receiving these agents prior to or during pregnancy.[21] The results of this analysis can be found in Table 5 below.

Table 5. Rate of Birth Defects in Infants Born to Mothers Receiving an Integrase Strand Transfer Inhibitor During Pregnancy[21]

	Total Outcomes	Live Births	Defect Cases	CNS Defects[a]	Neural Tube Defects
Any INSTI Exposure	2776	2551	86	8	1
Periconception	1647	1461	44	5	1
Any Dolutegravir Exposure	1231	1131	43	5	1
Periconception	649	571	18	2	1
Any Cabotegravir Exposure	5	3	1	0	0
Periconception	5	3	1	0	0
Any Bictegravir Exposure	254	234	5	2	0
Periconception	182	165	5	2	0
Any Elvitegravir Exposure	515	466	12	1	0
Periconception	413	367	11	1	0
Any Raltegravir Exposure	1055	990	34	1	0
Periconception	441	397	12	0	0

APR = antiretroviral pregnancy registry; INSTI = integrase strand transfer inhibitor; CNS = central nervous system

Note: Any Exposures include cases with missing trimester of exposure; [a] encephalocele are a subset of CNS defects and are counted separately from neural tube defects (no cases have been reported)

The NTD reported above following periconceptional exposure to dolutegravir was anencephaly.[21] The APR has not found a significant difference in prevalence of overall congenital abnormalities or by trimester of exposure, compared with population-based surveillance systems.

See Table 6 for an overview of additional observational cohorts reported.

Table 6. Overview of Observational Cohort Data on DTG-based 3DRs

Study	Data Sources	Pregnancies Exposed to DTG	Outcomes
US Database Analysis (2008-2019)[22]	MarketScan Commercial Claims & Encounters Database and Centers for Medicare & Medicaid Services Medicaid Data	2840	• One NTD reported with peri-conception or first trimester DTG exposure • No increased risk of NTDs in infants whose mothers were exposed to DTG during early pregnancy vs other ART and vs women without HIV • Higher risk of stillbirth (RR: 1.28; 95% CI: 1.07, 1.51) and pregnancy losses (RR: 1.59; 95% CI: 1.55, 1.63) among women living with HIV vs women living without HIV (Medicaid database)
DOLOMITE-EPPICC(birth outcomes reported by end 2019)[23]	NEAT-ID network and European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC)	550	• 508 live births: 326/508 had peri-conception DTG exposure, 36/508 were exposed to DTG later in the 1st trimester and 140/508 had DTG exposure in the 2nd or 3rd trimester • Birth outcomes: 508 live births, 5 still births, 27 spontaneous abortions and 18 induced abortions • 21 infants had ≥1 birth defect (3.9% prevalence of birth defects overall) • Among infants with peri-conception exposure to DTG, 4.6% (15/326) had a birth defect (95% CI: 2.6, 7.5) compared with 2.9% (4/140) of infants with earliest exposure in the 2nd or 3rd trimester (95% CI: 2.6, 7.5) • No NTDs reported
Brazil Cohort (1/1/15-5/31/18)[24]	Brazilian ART Database (SICLOM)	384	• Birth outcomes: 359 live births, 2 stillbirths and 23 abortions • Between January 2017 and March 2019, there were no NTDs with DTG and 18 congenital abnormalities • After study closure, 2 confirmed NTD outcomes in fetuses with peri-conception DTG exposure were reported
Fetal Biometry Study[25]	Cross-sectional analysis within Botswana cohort	176	• There were no significant differences in in fetal biometry (head circumference, biparietal diameter, abdominal circumference and femur length) between foetuses exposed to DTG vs EFV
Botswana birth anthropometrics[26]	Participants enrolled from Tshilo Dikotla & the Infant Gut Microbiome studies	158	• There were no significant differences in birth weight-for-age or length-for-age Z-scores between infants exposed *in utero* to DTG-based vs EFV-based regimens
PHACS Dynamic SMARTT cohort (as of 1/1/2020)[27]	US and Puerto Rico	120	• There were no substantial differences in risks of adverse birth outcomes between DTG-based and non-DTG-based regimens • Risk of any adverse birth outcomes ranged from 21.8%-27.7% across regimens

European analysis[28]	EPPICC, NEAT-ID, and Pharmacokinetics of newly developed Antiretroviral agents in HIV-infected pregnant women (PANNA)	101	• 84/101 pregnancies had outcomes, 16 were ongoing, and 1 was lost to follow-up
			  ○ 81 live births of 83 newborns; 1 spontaneous abortion; 1 induced abortion; 1 stillbirth
			• 58 (57%) involved exposure to DTG in the 1st trimester, 24 (24%) in the 2nd, and 18 (18%) in the 3rd
			• 4 (5%) live-born infants had a congenital anomaly; 11 (14%),13 (17%), 19% infants were born prematurely, had low birth weight, and were SGA, respectively
			  ○ 2 of the congenital anomalies identified were not considered defects according to the EUROCAT classification (Ankyloglossia and hyperpigmentation on back); bilateral hexadactyly, hands (father had same defect); patent foramen ovale with small left-to-right interatrial shunt

Study	Data Sources	Pregnancies Exposed to DTG	Outcomes
Canadian Surveillance Program (2007-2017)[29]	Canadian Perinatal HIV Surveillance Program (CPHSP)	80 (69 at conception)	• Of the 80 pregnancies with exposure to DTG, 4 had non-chromosomal congenital anomalies • No NTDs were reported
2 US Cohorts (1/1/2015-5/28/2018)[30]	Philadelphia, PA & Atlanta, GA	66	• Among the 57 women who delivered at the time of publication, 77% (n=44) had an undetectable HIV-1 RNA at delivery. The mean (SD) time to virologic suppression was 48 (23) days. • 59 infants (2 sets of twins): 2 infants were born with birth defects, 18 (32%) were born preterm (before 37 weeks gestation), and 9 (16%) were SGA (weight <10th percentile). ○ Birth defects reported were nonimmune hydrops fetalis (n=1, from twin pregnancy) and endocardial fibroelastosis with ventricular septal defect (n=1). • No NTDs or MTCT reported
Stockholm Pregnancy Cohort (2014-2017)[31]	General medical record TakeCare, pregnancy medical record Obstetrix, and the quality registry InfCare HIV	36 (14 peri-conception)	• Birth outcomes: 30 live births, 5 abortions (4 spontaneous abortions) and 1 lost to follow-up • No infant malformations were reported • 1 infant was SGA and no MTCT (as of publication in 2018)
NTD reports in Pharmacovigilance Safety Databases[32]	WHO VigiAccess Database	NR	• As of 8/21/18, 2747 total ADRs were reported for DTG: 50 were congenital, familial, and genetic ADRs; 7 of which were NTDs • 2940 ADRs were reported for ABC/DTG/3TC: 23 were congenital, familial, and genetic ADRs; 1 of which was NTD
	FDA FAERS Database		• As of 6/30/18, 2900 total ADRs were reported for DTG: 63 were congenital, familiar, and genetic ADRs; 6 of which were NTDs
	EU EudraVigilance Database		• As of 6/30/18, 2900 total ADRs were reported for DTG: 9 were congenital, familial, and genetic ADRs; none of which were NTDs
	UK MHRA Database		• As of 7/31/2018, 721 total ADRs were reported for DTG; non were congenital, familial and genetic ADRs, including NTDs

[a] Among patients tested between postpartum days 0-14

3TC = lamivudine; ABC = abacavir; ADR = adverse drug reaction; CI = confidence interval; DTG = dolutegravir; FTC = emtricitabine; MTCT = mother to child transmission; NTDs = neural tube defects; SD = standard deviation; SGA = small for gestational age; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate;

DOLUTEGRAVIR ELIMINATION IN HUMANS

The elimination half-life is the time it takes for the concentration of a drug to reduce by 50% and 5-times the terminal elimination half-life is the time at which a drug is 97% eliminated.[33] Dolutegravir has a terminal plasma half-life of approximately 14 hours; therefore, after 5 days dolutegravir is eliminated from plasma. The elimination half-life in tissues typically takes longer. There are no data on the elimination half-life in human tissues. However, data from studies in animals demonstrated that dolutegravir-related concentrations in tissues were typically less than those in blood and the elimination half-life of dolutegravir-related material from most tissues was up to 12 hours and by 28 days post-dose only bone and pigmented skin contained quantifiable concentrations of dolutegravir-related material.

Based on the elimination half-life of dolutegravir in human plasma and animal tissues, essentially complete elimination of dolutegravir from the blood and tissues is expected 30 days or one month after stopping dolutegravir treatment.[33]

Lactation

Dolutegravir is excreted in human milk in small amounts.[34] In an open-label randomized study in which HIV-infected treatment-naïve pregnant women were administered a DTG-based regimen until 2 weeks post-partum, the median (range) DTG breast milk to maternal plasma ratio was 0.033 (0.021 to 0.050).

LOWER LEVELS OF EVIDENCE

There are several case reports and case series published describing the use of dolutegravir in pregnant women and during the postpartum period.[35-47]

ONGOING RESEARCH

There are several company-sponsored and collaborative studies underway that are designed to evaluate the safety and pharmacokinetics of dolutegravir in pregnant women.

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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