P-574

Extrapolating Expected Efficacy, Safety, and Pharmacokinetics (PK) of Dolutegravir/Lamivudine (DTG/3TC) in Pregnant People Living With HIV-1 From Pregnancy Data With Combination DTG and/or 3TC Antiretroviral Therapies

William R. Short,[1] **Parul Patel**,[2] **Gustavo Verdier**,[3] **Ana Puga**,[2] **Andrew Weber**,[2] **Leigh Ragone**,[2] **Eva Fernvik**,[4] **Vani Vannappagari**,[2] **V. Paul DiMondi**,[2] **Bryn Jones**[5]

[1]Department of Medicine, Division of Infectious Diseases, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]ViiV Healthcare, Durham, NC, USA; [3]ViiV Healthcare, Montréal, Canada; [4]ViiV Healthcare, Stockholm, Sweden; [5]ViiV Healthcare, Brentford, UK

Presenting author:
William R. Short
Perelman School of Medicine, University of Pennsylvania
Medical Arts Building
3801 Filbert Street, Suite 103
Philadelphia, PA, USA 19104
William.Short@pennmedicine.upenn.edu
215-662-8693

Key Takeaways

- **Minimizing fetal exposure to unnecessary drugs is a guiding principle during pregnancy**
- **Efficacy of ARVs for treatment of pregnant people can be extrapolated from evidence of efficacy in non-pregnant adults following confirmation of adequate PK during pregnancy**
- **PK from studies of DTG-based 3DRs containing 3TC in pregnancy reliably predict the PK of DTG/3TC as a 2DR during pregnancy**
- **DTG and 3TC are anticipated to achieve similar therapeutic PK exposures for maintenance of parental virologic suppression, both when used as a 3DR or 2DR in pregnancy**
- **The totality of efficacy, safety, and PK data on DTG-based 3DRs with 3TC in pregnancy is extensive and may help support the management of people during pregnancy who are using DTG/3TC or may become pregnant while taking DTG/3TC**

Introduction

- DTG/3TC is a simplified, once-daily, 2DR developed to address an unmet need for a highly effective and well-tolerated antiretroviral therapy (ART) with potentially reduced short- and long-term toxicities associated with a third or fourth drug. This may be especially important in pregnancy to minimize fetal exposure to unnecessary drugs
- Data on DTG/3TC use among pregnant people with HIV-1 are limited; however, safety and PK data on individual components are extensive from DTG- and 3TC-containing 3DRs
- Department of Health and Human Services (DHHS) perinatal treatment guidelines do not recommend DTG/3TC as an initial treatment option in pregnancy, despite DTG 3DRs being recommended as a preferred first-line option in pregnancy. However, they state pregnant persons who present to care virologically suppressed on DTG/3TC can continue their current treatment with more frequent viral load monitoring

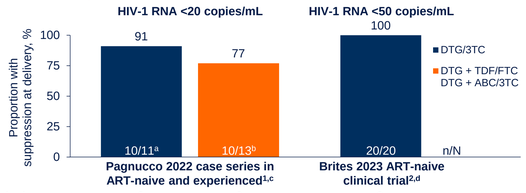
Methods

- Randomized trial data on efficacy and PK from pregnant people with HIV-1 using DTG-based 3DRs or 2DRs were used to extrapolate anticipated DTG/3TC 2DR efficacy, safety, and PK in pregnancy
- Literature searches were performed using PubMed to identify peer-reviewed articles evaluating DTG and/or 3TC use in pregnant people with HIV-1 using “dolutegravir AND/OR lamivudine AND pregnancy” as search terms between January 2012 and November 2023 for DTG and between January 1998 and November 2023 for 3TC
- Articles were reviewed and those with efficacy, safety, PK, vertical transmission, and/or birth outcomes in pregnant people with HIV-1 were extracted. Searches were supplemented with key manuscripts, conference presentations, and reports on DTG/3TC use and birth outcomes with DTG-based ART
- Clinical utility of DTG/3TC in pregnancy was evaluated in context of perinatal treatment guideline recommendations

Results

- Overall, 686 articles were found, of which 9/194 DTG and 8/492 3TC articles were retained. These were supplemented with an additional 6 manuscripts, 3 conference reports, and the Antiretroviral Pregnancy Registry (APR) Interim Report from December 2023 (data through July 2023)
- 2 studies (1 clinical trial and 1 case series) reported use of DTG/3TC in pregnancy. Both found high virologic suppression rates (97% [30/31]) to HIV-1 RNA <20 or <50 copies/mL when initiated prior to conception (Pagnucco only) or between 14 and 28 weeks of gestational age, no events of vertical transmission (Figure 1), and no new safety signals, consistent with the use of DTG-based 3DRs in pregnancy

Figure 1. Efficacy of DTG/3TC in Pregnant People With HIV-1



[a]1 participant naive to ART had HIV-1 RNA 53 copies/mL at delivery. [b]1 participant had HIV-1 RNA 35 copies/mL at delivery, and 2 had HIV-1 RNA >1500 copies/mL at delivery. [c]Participants were either ART-naive (n=3/11 on DTG/3TC; 4/13 on DTG + TDF/FTC or DTG + ABC/3TC) or ART-experienced initiating therapy. [d]Participants were ART-naive initiating DTG/3TC between 14 and 28 weeks of gestational age.

- DTG/3TC efficacy data, although limited, are consistent with data reported for DTG 3DRs containing 3TC or FTC (Table 1)

Table 1. Efficacy Outcomes in Randomized Clinical Trials of DTG 3DRs in Pregnant People With HIV-1 Naive to ART

Study	Gestational age at study entry	Regimen	Reported parental viral load at delivery, copies/mL: % (n/N)	Reported vertical transmission rate	Time point(s) for vertical transmission assessment
DTG 3DR: dolutegravir + lamivudine or emtricitabine + 3rd NRTI vs efavirenz + 2 NRTIs					
Waitt 2019[3] (DOLPHIN-1)	28 to 36 weeks	DTG + TDF/3TC or TDF/FTC EFV + TDF/3TC or TDF/FTC	<50: 69% (20/29)[a] <50: 39% (12/31)[a]	NR	—
Kintu 2020[4] (DOLPHIN-2)	At least 28 weeks	DTG + TDF/3TC or TDF/FTC EFV + TDF/3TC or TDF/FTC	<50: 74% (89/120) <50: 43% (50/117)	2% (3/123) 0% (0/119)	Birth to 72 weeks
Lockman 2021[5] (IMPAACT 2010/VESTED)	14 to 28 weeks	DTG + TAF/FTC or TDF/FTC EFV/TDF/FTC	<200: 98% (395/405) <200: 91% (182/200)	n=2[b] n=0[b]	Birth to 28 days

[a]Assessed 2 weeks postpartum. [b]Of 617 live-born infants, 561 had at least 1 HIV-1 test result available; N not reported for each treatment group.

- Efficacy and vertical transmission rates with 3TC have been studied in >3000 pregnant people with HIV-1 in a 3DR containing 2 NRTIs (n=285), INSTI (no DTG) + 1 NRTI (n=190), or NNRTI + 1 NRTI (n >600), or (less frequently) with DTG only (n=31)
- 3TC-containing 3DR studies, excluding DTG, have reported achievement of parental virologic suppression rates at delivery ranging from 25% to 98% (viral load <500, ≤400, or <50 copies/mL) when initiated at 12 to 36 weeks of gestation and vertical transmission rates from 0% to 3%
- In 2 studies using dual 3TC + zidovudine in pregnancy, 14% (n=88) achieved HIV-1 RNA <500 copies/mL at delivery; however, in the second study, ~75% achieved HIV-1 RNA <500 copies/mL at delivery

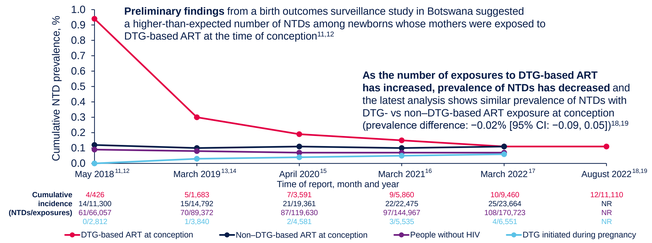
Table 2. Summary of Safety Events Reported With DTG-Based Regimens in Studies of Pregnant People With HIV-1

Study	Design	Regimen(s), N	Time point(s) assessed	Safety profile
Brites 2023[2] (PREGNANT)	Open-label, non-randomized, pilot	DTG/3TC (N=20)	Treatment initiation between 14-28 weeks of gestation through 6 weeks postpartum	No AEs reported
Mulligan 2018[6] (IMPAACT P1026s)	Open-label, non-randomized, PK	DTG-based 3DR (N=29)[a]	20 weeks of gestation through 6-12 weeks postpartum	Grade 3 AE: n=8 (28%)[b]
Waitt 2019[3] (DOLPHIN-1)	Open-label, randomized, PK	DTG + TDF/FTC or TDF/3TC (N=29) EFV + TDF/FTC or TDF/3TC (N=31)	7, 14, and 28 days after treatment initiation (between 28-36 weeks of gestation) and 56 days after treatment initiation if delivery had not taken place; 14 days after delivery; and 6 months postpartum	≥1 SAE: n=2 (7%)[c] ≥1 SAE: n=1 (3%)[d]
Kintu 2020[4] (DOLPHIN-2)	Open-label, randomized	DTG + TDF/FTC or TDF/3TC (N=137) EFV + TDF/FTC or TDF/3TC (N=131)	7 and 28 days after treatment initiation (~28 weeks of gestation), 36 weeks of gestation (if applicable), first postpartum visit (0-14 days postpartum), and up to 6 weeks thereafter	≥1 SAE: n=30 (22%)[e]; ≥1 drug-related SAE: n=1 (<1%) ≥1 SAE: n=14 (11%)[f]; ≥1 drug-related SAE: n=0
Bollen 2021[7] (PANNA)	Open-label, non-randomized, PK	DTG-based ART (N=17)	~33 weeks of gestation to 4-6 weeks postpartum	Any AE: n=7 (41%); 11 AEs, including 4 SAEs[g] considered unlikely or not related to DTG
Lockman 2021[5] (IMPAACT 2010/VESTED)	Open-label, randomized	DTG + TAF/FTC (N=217) DTG + TDF/FTC (N=215) EFV/TDF/FTC (N=211)	Every 4 weeks after randomization (14-28 weeks of gestation) through 14 days postpartum	Any grade ≥3 clinical or lab AE: n=45 (21%) Any grade ≥3 clinical or lab AE: n=56 (26%) Any grade ≥3 clinical or lab AE: n=47 (22%)

[a]Participants primarily received DTG with ABC/3TC (69%) or TDF/FTC (17%). [b]Low hemoglobin (n=3); pre-eclampsia (n=2); and pre-term labor, nausea/vomiting, cesarean wound infection/fever, blurry vision/headache, low albumin, and proteinuria (n=1 each). [c]1 case of decreased hemoglobin (not drug related). 1 case of malaria and urinary tract infection (possibly drug related); stillbirth (unlikely to be drug related); and increased ALT and bilirubin, hypokalemia, and hyponatremia (possibly drug related). [d]1 case of hypertension and pre-eclampsia (unlikely to be drug related). [e]Includes 3 stillbirths. [f]Includes 1 stillbirth. [g]1 intrauterine fetal death; 2 hospital admissions due to suspected pre-eclampsia/hemolysis, elevated liver enzymes, and low platelet count syndrome; and 1 congenital abnormality (hypospadias).

- Overall, first-trimester exposure to DTG and 3TC have not been shown to increase the risk of major birth defects, including neural tube defects (NTDs). 3TC use during pregnancy has not been associated with adverse maternal, obstetric, or infant outcomes[8,9]
- Reported tolerability and safety specific to DTG/3TC use in pregnancy are limited; however, the anticipated safety of a DTG/3TC 2DR can be supported by favorable safety reported in >100 pregnant people with HIV-1 using DTG 3DRs containing 3TC during pregnancy (Table 2). Worldwide, >880,000 pregnant people are estimated to have received TDF/3TC/DTG (TLD) in 2022[10]

Figure 2. Summary of Birth Outcomes Surveillance Studies

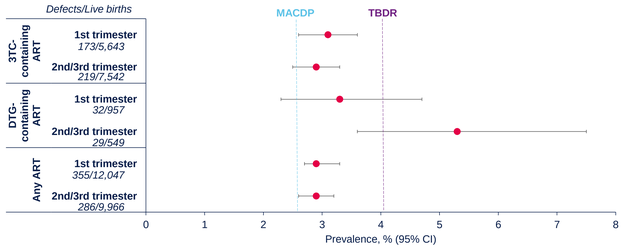


In the Eswatini birth surveillance study, **NTD prevalence was the same** (0.08%) for people on DTG at conception as people without HIV[20]

People's HIV-1 status and conception regimen	Live births and stillbirths	NTD (%; 95% CI)
Total from subgroups with birth defects	24,599	19 (0.08; 0.05-0.12)
HIV-negative	17,285	13 (0.08; 0.04-0.13)
All people with HIV-1	7,308	6 (0.08; 0.04-0.18)
DTG at conception	4,902	4 (0.08; 0.03-0.21)
EFV at conception	1,320	2 (0.15; 0.04-0.55)
No ART at conception (newly initiated on ART during pregnancy)	1,092	0

- As of July 2023, combined reports from Tsepamo (Botswana)[17] and Eswatini[20] birth outcomes surveillance studies reported >14,000 recorded births among people on DTG at conception with 14 NTDs reported[9]
- Both studies suggest no increased risk of NTDs from pregnancies exposed to DTG-based ART at conception vs non–DTG-based ART (EFV) at conception and vs people living without HIV-1 (Figure 2)[9,17,20]

Figure 3. Birth Defects Prevalence by Earliest Trimester of Exposure to ART (APR Through 21 July 2023)[9]



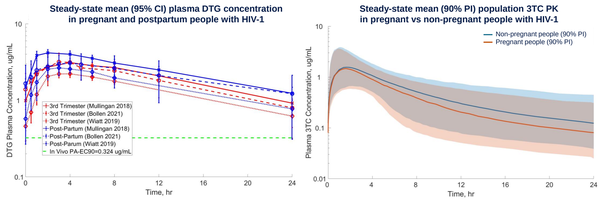
MACDP, Metropolitan Atlanta Congenital Defects Program; TBDR, Texas Birth Defects Registry.

- As of July 2023, birth defects were reported in 32/957 (**3.3%**) and 29/549 (**5.3%**) DTG exposures in the **first** and **second/third trimesters**, respectively
- These rates were comparable to **population-expected rates** from birth defects registries of **2.76%** (Atlanta) and **4.19%** (Texas)
- **The APR has not found an increased risk of major birth defects in people exposed to DTG or 3TC (overall or by trimester of exposure) compared with population-based surveillance systems (Figure 3)[9]**

DTG and 3TC PK During Pregnancy

- Currently, there are no data on DTG/3TC 2DR PK in pregnancy; however, PK are anticipated to be comparable regardless of whether administered as a 2DR or 3DR
- **PK from studies of DTG-based 3DRs containing 3TC reliably predict DTG/3TC PK as a 2DR for the following reasons:**
  1. **Both regimens share DTG and 3TC**
  2. **Absence of drug-drug interaction between DTG and 3TC or with third ART agent evaluated in pregnancy studies**
  3. **PK of DTG and 3TC separately have been well established in pregnancy**
- No dose adjustment is required for DTG or 3TC during pregnancy based on 3 DTG PK and 2 3TC PK studies in pregnant people with HIV-1 (Figure 4)
- Bioequivalence of DTG/3TC single-tablet regimen compared with individual components of DTG + 3TC was previously demonstrated in non-pregnant adults, further supporting interchangeability[21]

Figure 4. PK Parameters of DTG and 3TC in Pregnant vs Non-pregnant Adults



	n	DTG (50 mg QD) AUC$_{0\text{-}24,SS}$	DTG (50 mg QD) C$_{24,SS}$	n	3TC (300 mg QD) AUC$_{0\text{-}24,SS}$	3TC (300 mg QD) C$_{avg,SS}$	3TC (300 mg QD) C$_{24,SS}$
Adult people with HIV-1	>350[22]	53.6 (34.6-82.9)[a]	1.11 (0.54-2.28)[a]	60[18]	8.7 (5.6-14.9)[a]	0.36 (0.24-0.62)[a]	0.04 (0.02-0.09)[a]
				14[20]	10.1 (9.4-10.9)[d]	0.42 (0.39-0.45)[d]	
				6[21]	10.9 (8.3-14.2)[d]	0.45 (0.35-0.59)[d]	
Pregnant people with HIV-1	28 (3T)[3]	35.3 (19.2-67.9)[b]	0.64 (0.19-3.09)[b]	PopPK	10.3 (6.6-16.1)[e]	0.43 (0.28-0.67)[e]	0.08 (0.02-0.31)[e]
	15 (3T)[7]	40.8 (23.3-71.4)[a]	0.68 (0.20-2.26)[a]				
	28 (3T)[6]	49.2 (36.4-62.0)[c]	0.93 (0.68-1.34)[c]				
	15 (2T)[6]	47.6 (33.4-63.7)[c]	0.73 (0.63-1.34)[c]				
Postpartum or non-pregnant people with HIV-1	17[3]	40.1 (22.8-59.6)[b]	0.77 (0.35-1.21)[b]	PopPK	12.6 (8.1-19.7)[e]	0.53 (0.34-0.79)[e]	0.13 (0.04-0.44)[e]
	10[7]	47.0 (24.2-91.2)[a]	1.03 (0.37-2.84)[a]				
	22[6]	65.0 (47.8-88.4)[c]	1.28 (0.80-1.95)[c]				

[a]Geometric mean (estimated 90% PI). [b]Geometric mean (range). [c]Median (IQR). [d]Geometric mean (90% CI). [e]Simulated geometric mean (90% PI) from model in Benaboud et al.[23]

Conclusions

- DTG/3TC is anticipated to be effective and tolerated for both parental health and prevention of vertical transmission with fetal exposure to fewer drugs
- Pregnancy is not anticipated to differentially impact DTG/3TC exposures compared to when used in a 3DR
- Individually, DTG and 3TC are part of preferred regimens for use in pregnancy in the DHHS perinatal treatment guidelines. The guidelines support DTG/3TC therapy for pregnant persons who present to care virologically suppressed with more frequent viral load monitoring
- Although there are limited data on the use of DTG/3TC 2DR in pregnancy, the totality of data with DTG and 3TC in pregnancy as 3DRs is extensive and may help support the management of people during pregnancy

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