The effect of pregnancy on the pharmacokinetics of total and unbound dolutegravir and its main metabolite in women living with HIV

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Abstract

Background

Pharmacokinetic and efficacy data on dolutegravir in HIV-positive pregnant women are still limited but needed to support its use as one of the preferred antiretroviral agents.

Methods

Within the multi-center "Pharmacokinetics of ANtiretroviral agents in HIV-infected pregNAnt women" (PANNA) study, HIV-positive pregnant women using dolutegravir once-daily (50mg, with food) underwent 24h pharmacokinetic profiling in third trimester (3T) and postpartum (PP). Dolutegravir exposure in 3T was considered adequate if geometric mean unbound – pharmacologically active – minimal plasma concentrations ($C_{min,\ unbound}$) and ≥90% of individual $C_{min,\ unbound}$ levels were >0.85 µg/L, the proposed 90% inhibitory concentration (IC_{90}) for unbound dolutegravir. Geometric mean ratios (GMR) with 90% confidence intervals (CI) for comparison of total and unbound pharmacokinetic parameters in 3T and PP were calculated, including the metabolic ratio for dolutegravir-glucuronide. Safety and virological data were collected.

Results

Twenty-three women (74% black) were enrolled (35 evaluable pharmacokinetic profiles; 20 in 3T, 15 PP). In 3T, geometric mean (coefficient of variation,%) $C_{min,\ unbound}$ was 2.87 (87) µg/L and 93% of individual $C_{min,\ unbound}$ levels were >0.85 µg/L. GMRs (90%CI) in 3T versus PP were: area under the curve ($AUC_{0\text{-}24h}$), 81 (68-97)%; C_{max}, 85 (72-101)%; and for trough concentrations 69 (54-88)%, based on total dolutegravir concentrations. Four serious adverse events were reported, unlikely related to dolutegravir. HIV PCR test was negative in 19/22 infants (3 unknown).

Conclusions

Pharmacokinetic changes for dolutegravir in late pregnancy are not clinically relevant and support the use of dolutegravir 50mg once-daily with food in pregnancy.

Clinical Trials Registration NCT00825929

Keywords HIV, MTCT, dolutegravir, pharmacokinetics, pregnancy.

INTRODUCTION

For treatment of HIV-infected pregnant women guidelines recommend antiretroviral therapy (ART) during the entire course of pregnancy for the benefit of the mother and to prevent mother to child transmission (MTCT) of HIV.[1] ART reduces the risk of MTCT from pregnant and non-breastfeeding women to the unborn child from 20-45% to less than 1%.[2, 3] The World Health Organization (WHO) has selected the integrase-inhibitor dolutegravir as preferred antiretroviral agent for use in first-line combined ART in all people living with HIV. This includes pregnant HIV-positive women and those of childbearing potential. In 2018 preliminary data from a birth outcome surveillance study in Botswana detected a 0.9% risk of neural tube defects (NTDs) in 426 infants delivered by women receiving dolutegravir around conception or early in the first trimester of pregnancy. This was considered a substantial risk relative to 0.1% NTDs observed with other antiretrovirals. However, more recent data from this study, which now includes over 9,000 exposures to dolutegravir at the time of conception, has shown no difference in the risk of neural tube defects in infants born to mothers taking dolutegravir compared to other antiretroviral regimens;; 10 cases in 9,460 deliveries (0.11%; 95% CI 0.06%, 0.19%) to mothers taking dolutegravir-containing regimens at the time of conception compared to 25 cases in 23,664 deliveries (0.11%: 95% CI 0.07%, 0.16%) to women exposed to non-dolutegravir regimens at the time of conception. [4-6]

During the course of pregnancy, many physiological changes occur that may alter exposure to antiretroviral drugs, most often resulting in reduced drug levels with a risk for compromised efficacy.[7] For dolutegravir, an adequate exposure-response relationship has been established.[8] Pharmacokinetic data can therefore serve as predictor for efficacy outcomes (suppression of viral inhibition), and thus inform us on appropriate dose adjustments in pregnancy.

In pregnancy, a reduction in plasma proteins (e.g. albumin[9]) might cause total dolutegravir plasma concentration – the sum of the plasma protein bound and unbound drug concentration – to decrease. However, only the unbound portion of a drug ('free-drug') can reach target sites through diffusion or active transport and exerts its biological effect. Therefore, in case of highly protein bound drugs such as dolutegravir (99.5%), and in the setting of pregnancy, protein unbound concentrations are of particular interest.[10]

Our aim was to provide dosing recommendations for dolutegravir use in pregnancy based on total and unbound dolutegravir plasma concentrations. In addition, we aimed to investigate the impact of pregnancy-related physiological changes on dolutegravir metabolism and therefore quantified inactive dolutegravir-glucuronide, which is dolutegravir's main metabolite. This study is part of the European "Pharmacokinetics of ANtiretroviral agents in HIV-infected pregNAnt women" (PANNA) network, that

was established to study the pharmacokinetics of newly developed antiretroviral drugs during pregnancy, including dolutegravir.

METHODS

Study design and participants

This was an open-label, non-randomized, multi-center, within-patient, pharmacokinetic phase-IV study in HIV-positive pregnant women in Europe (*ClinicalTrials.gov* #NCT00825929), coordinated by the PANNA network study group (www.pannastudy.com). Pregnant HIV-positive women (aged ≥18 years old) using dolutegravir 50mg once-daily as part of their ART, for at least 2 weeks prior to the first pharmacokinetic assessment in third trimester of pregnancy, were eligible for inclusion. Exclusion criteria were having a relevant history or current medical condition that might interfere with pharmacokinetics on the level of absorption, distribution, metabolism or elimination, inability to understand the nature and extent of the study and the procedures required, and grade III/IV anemia (i.e. hemoglobin <4.6 mmol/L or 7.4 g/dL). The study was conducted in compliance with ethical principles as stated in the Declaration of Helsinki and conducted and documented in accordance with the principles of Good Clinical Practice (GCP). The study was approved by the medical ethical committee of the participating centers and by national authorities if applicable.

The primary objective of this study was to evaluate and compare unbound and total dolutegravir drug concentrations within the third trimester of pregnancy (approximately at week 33) versus at least 2 weeks postpartum (ideally 4-6 weeks postpartum). Secondary objectives were to report safety and efficacy outcomes for dolutegravir-based regimen in pregnant women, to assess dolutegravir-glucuronide metabolite concentrations in pregnancy and postpartum, to assess fetal exposure to dolutegravir at time of delivery, and to report safety and efficacy outcomes for infants exposed to dolutegravir through their HIV-infected mothers.

Procedures

Screening and enrollment procedures within ≤4 weeks upon inclusion (first pharmacokinetic assessment) consisted of obtainment of medical history, physical examination and laboratory tests (serum biochemistry and hematology, qualitative urinalysis, HIV-1 RNA viral load and CD4 cell count).

At pharmacokinetic assessments, EDTA blood samples were collected at t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24h after observed intake of ART, including dolutegravir 50mg, with food (650 kcal; 30 g fat) to generate steady-state pharmacokinetic profiles in third trimester and postpartum.

Matching cord blood (CB) and maternal blood (MB) plasma samples were taken at delivery (if feasible) to estimate placental transfer. Unbound dolutegravir concentrations were measured in plasma

samples representing the highest (C_{max}) and lowest (C_{min}) total dolutegravir plasma concentrations in individual total dolutegravir plasma concentration-time curves.

Plasma obtained from EDTA blood samples was stored at -18°C or lower until shipment under frozen conditions to the laboratory of the Department of Pharmacy at the Radboud university medical center (Nijmegen, the Netherlands) for quantification of total and unbound dolutegravir and glucuronide-metabolite concentrations. Total dolutegravir plasma concentrations were measured with a validated ultra performance liquid chromatography - tandem mass spectrometry (UPLC-MS/MS) quantification method.[11] The dolutegravir assay was externally validated through the International Interlaboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma as well as by the Clinical Pharmacology Quality Assurance and Quality Control Program (CPQA). Unbound concentrations were obtained by ultrafiltration and measured with an UPLC-MS/MS method with a lower limit of quantification (LLOQ) of 0.5 µg/L. ^{2}H-nevirapine (*m/z* 271 → 230) served as internal standard for quantification of dolutegravir-glucuronide by UPLC-MS/MS (*m/z* transition 596 → 420) and the linear calibration range in plasma was 0.005 – 1.0 mg/L.

At each visit, adverse events were evaluated and HIV-1 RNA viral load was measured. Blood samples for safety and efficacy evaluations were obtained on pharmacokinetic sampling days and - if part of local standard procedures for routine patient care - at time of delivery, and were analyzed at local laboratories. All maternal adverse events that occurred during the study were recorded and graded according to the Division of AIDS toxicity table.[12] Efficacy outcomes were HIV-1 RNA viral load <50 copies/mL measured in third trimester or at delivery. Infant outcomes, including birth weight, gestational age (GA) at birth, congenital abnormalities, and HIV infection status (by detection of HIV nucleic acids) were collected.

Statistical and pharmacokinetic analysis

Sample size calculation was based on an expected intrasubject variability of dolutegravir AUC of ≤35%. A sample size of 14 (number of pairs) was required to achieve a power of 80% and a level of significance of 10% (two sided), for detecting a mean of the differences of 25% (for a geometric mean ratio confidence interval of 0.75-1.33) between pairs and assuming an intra-subject variation of 35%.

To account for possible drop-outs our aim was to include 22 patients. Pharmacokinetic parameters were derived from individual plasma concentration-time curves and included for total dolutegravir: the area under the plasma concentration–time curve from 0 to 24 hours after intake ($AUC_{0–24h}$); C_{max},; the time to reach C_{max} (T_{max}); C_{min}; the concentration at 24 hours after dosing (C_{trough}); the apparent volume of distribution (Vd/F); the apparent oral clearance (CL/F), and the apparent elimination half-life ($T_{1/2}$). For dolutegravir-glucuronide, AUC_{0-24h} was calculated. Fraction unbound (f_u) was calculated

with the formula; f_u = unbound concentration/total concentration * 100%. Non-compartmental pharmacokinetic (NCA) analysis and calculation of descriptive statistics for total dolutegravir and dolutegravir-glucuronide pharmacokinetic parameters was conducted with Phoenix® WinNonlin® 64 version 8.1 (Certara, Inc., Princeton, USA).

The unbound minimal plasma concentration ($C_{min, unbound}$) was considered adequate if geometric mean $C_{min, unbound}$ in third trimester remained above the proposed minimal threshold of 0.85 µg/L for unbound dolutegravir concentrations, and if at least 90% of individual $C_{min, unbound}$ were above this threshold. The threshold of 0.85 µg/L represents an estimation of the protein unadjusted *in vitro* IC_{90} and was derived from the *in vitro* protein adjusted minimal inhibitory concentration (IC_{90}) for dolutegravir (152 nM; 0.064 mg/L) using the fold potency shift with 100% human serum.[13] In addition, individual total plasma concentrations below the *in vivo* minimal effective concentration (EC_{90}) of 0.32 mg/L were summed. This EC_{90} was derived from the EC_{50} found by Min *et al.*[8] A linear mixed-effects model (bioequivalence test within WinNonlin®) with treatment (pregnancy or postpartum) as fixed-effect and including a random effect for patient was used for estimation of geometric mean ratios (GMR) and 90% confidence intervals (CIs) of pharmacokinetic parameters in pregnancy versus postpartum. Median (inter quartile range, IQR) molar AUC_{0-24h} ratios of dolutegravir-glucuronide/dolutegravir and geometric mean (IQR) cord blood-to-maternal blood plasma concentration ratios were calculated.

RESULTS

Twenty-three HIV-positive pregnant women on dolutegravir-based ART from eight European hospitals provided informed consent and were enrolled in the PANNA study between June 2015 and April 2022. Twenty-two women underwent at least one pharmacokinetic assessment, resulting in a total of 35 evaluable pharmacokinetic profiles (20 in third trimester and 15 postpartum, Figure 1).

For one patient no pharmacokinetic assessment was done due to COVID lock-down in 2020, her pregnancy was terminated due to trisomy 13. The data of one patient were not evaluable because of DTG intake prior to collection of curve was <20 hours.

Patient demographics and characteristics, including pregnancy outcomes are presented in Table 1. At time of conception, 21/23 (91%) women were aware of their positive HIV status and two were diagnosed with HIV after conception, at 12 and 16 weeks of GA. One of these patients initiated dolutegravir-based ART at 14 weeks GA and the other patient initiated dolutegravir-based ART in late pregnancy at 36 weeks of GA. Median (range) total time on dolutegravir-based ART between conception and delivery was 30.8 (3.0-41.1) weeks.

Use of concurrent medication, either ART or non-HIV related, that could possibly influence dolutegravir exposure included ritonavir boosted darunavir in two patients and cation containing supplements in five patients. At the third trimester assessment (34 weeks of GA) one patient suffered from cholestasis of pregnancy syndrome, but alanine transaminase (ALT) levels remained below the upper limit of normal, bile acid level was unknown, gamma-glutamyltransferase (GGT) level was 973 IU/L and alkaline phosphatase (ALP) was 263 U/L. Median (range) plasma albumin levels were 36.5 (25-40) g/L (n=12; 10 unknown) in third trimester and 40 (36-44) g/L (n=10; 12 unknown) postpartum.

Pharmacokinetics

The pharmacokinetic assessment in the third trimester and postpartum took place at a median (range) GA of 33.4 (30.9-38.1) weeks and 6 (2.9-7.4) weeks after delivery, respectively. Mean dolutegravir plasma concentration-time profiles of dolutegravir 50mg QD during third trimester and postpartum are shown in Figure 1. Descriptive summary statistics for dolutegravir total, unbound and dolutegravir-glucuronide pharmacokinetic parameters are given in Table 2.

The geometric mean $C_{min,\ unbound}$ (2.87 μg/L) in the third trimester of pregnancy was well above the proposed *in-vitro* protein unadjusted IC_{90} of 0.85 μg/L. Figure 2 depicts the individual changes between the third trimester and postpartum in minimal unbound concentrations and total trough plasma concentrations. Individual $C_{min,\ unbound}$ levels were above the IC_{90} in 14/15 (93%) patients in third trimester and in 10/10 (100%) of patients at time of the postpartum visit. The sub-therapeutic $C_{min,\ unbound}$ (0.79 μg/L) in third trimester corresponded with a total plasma C_{trough} of 0.64 mg/L, which was above the EC_{90} (0.32 mg/L) for total plasma concentrations; HIV-1 RNA was undetectable in this woman and serum albumin level unknown.

The third trimester geometric mean total C_{trough} (0.71 mg/L) was also well above the EC_{90} of 0.32 mg/L. Two patients had C_{trough} values <0.32 mg/L in the third trimester (0.11 mg/L while on dolutegravir with abavir/lamivudine and 0.28 mg/L while on dolutegravir with ritonavir-boosted darunavir), but HIV-1 RNA viral load was undetectable in both women. Both patients showed liver enzyme abnormalities at the third trimester visit. None of the patients had a subtherapeutic dolutegravir level postpartum.

Exposure to dolutegravir, expressed as $AUC_{0\text{-}24h}$ and C_{max}, based on total dolutegravir plasma concentrations, were lower in the third trimester, however, less than 20% lower than postpartum (Table 2). Meanwhile, the apparent elimination half-life decreased by 16% in the third trimester of pregnancy compared to postpartum. In line with this, total dolutegravir trough plasma concentrations were an estimated 31% lower in pregnancy versus postpartum. f_u was an estimated 20% higher in the third trimester versus postpartum. The estimated GMR (90% CI) for $C_{min,\ unbound}$ in third trimester versus postpartum was 0.86 (0.50-1.48). Thirteen paired umbilical cord blood and maternal blood

samples were collected. The geometric mean (IQR) cord blood-to-maternal blood plasma concentration ratio for dolutegravir was 1.38 (1.11-1.50).

Maternal and infant safety and efficacy outcomes

Nine patients reported a total of 16 adverse events, including 6 serious adverse events (SAE), that were considered unlikely or not related to dolutegravir by the treating physician. SAEs included one intrauterine fetal death (at 34 weeks of pregnancy, which was probably caused by cholestasis of pregnancy syndrome), one trisomy 13, leading to termination of pregnancy for medical reasons, two hospital admissions due to suspected pre-eclampsia/HELLP-syndrome, and one congenital abnormality (hypospadias) (unlikely to be related to dolutegravir exposure as other cases in the child's family were reported), one polydactyly. Where reported molecular tests for HIV were negative (n=19; 3 unknown. Birth weight of two infants (2,120 g and 2,305 g) was considered low (<2,500 g).

DISCUSSION

This was the first study that evaluated unbound dolutegravir concentrations and dolutegravir-glucuronide metabolite levels, besides total plasma concentrations, in the third trimester of pregnancy and postpartum. In our research total dolutegravir plasma concentrations decreased and pregnancy seemed to have more impact on these total concentrations than on pharmacologically active minimal unbound dolutegravir concentrations. This underlines the importance of measuring unbound drug concentrations in special situations where pharmacokinetics might be altered, such as during pregnancy. In this study, two women (12%) had unbound or total concentrations below target, but all women in the third trimester/delivery had an undetectable HIV-1 RNA viral load (<50 copies/mL). In addition, dolutegravir was well tolerated and MTCT of HIV was prevented in all cases. Taken together, the results of this study support the use of standard once-daily 50mg dolutegravir (with food) during pregnancy in HIV-positive women.

In our small study population, dolutegravir was generally safe during pregnancy and postpartum. Note, one stillbirth was reported after initiation of dolutegravir in the second trimester of pregnancy and was attributed to pregnancy-related cholestasis syndrome as reported by the treating physician. Out of seven women in this study who initiated dolutegravir-based ART before conception or in the first trimester none of the infants born were diagnosed with NTDs. As mentioned, although dolutegravir was previously linked with an increased risk for NTDs in infants born to mothers with pre-conception and first trimester exposure to dolutegravir[14, 15], new evidence, included updated data from the Tsepamo study which originally reported the association, has shown no increased risk of NTDs with DTG-based ART compared with other regimens. Based on the latest data from the Tsepamo study, the

risk for NTDs with the use of dolutegravir from conception is 1.1 per 1000 deliveries versus 1.1 in 1000 with non-DTG ART regimens).[5] WHO updated their guidelines based on these data and currently recommends the use of dolutegravir-based ART as preferred treatment for all populations, including pregnant women and those of childbearing potential.[4]

Pharmacokinetic results reflect appropriate exposure to dolutegravir in pregnancy as unbound minimal plasma concentrations seemed equal in third trimester versus postpartum. In addition, in third trimester, >90% of individual unbound minimal plasma concentrations were above the proposed threshold and total trough plasma concentrations showed a non-clinically relevant decrease. This interpretation is supported by the relatively wide therapeutic window of dolutegravir.[16] A 31% decrease in total trough plasma concentration resulting in geometric mean C_{trough} of 0.71 mg/L in the third trimester of pregnancy is therefore considered not clinically relevant.

Our data are in line with other studies on dolutegravir pharmacokinetics during pregnancy.[17] Mulligan *et al.* (IMPAACT P1026s protocol) also found similar median $AUC_{0\text{-}24h}$ (49.2 µg*h/mL) in third trimester versus postpartum (65.0 µg*h/mL), and a 34% decrease in trough concentrations in the third trimester.[18] In a smaller pharmacokinetic analysis by Wait *et al.* $AUC_{0\text{-}24h}$, C_{max} and C_{trough} were 39.4 mg*h/L, 2.6 mg/L and 0.8 mg/L (n=7), respectively, in pregnant women enrolled late in pregnancy in antenatal clinics in Cape Town and Kampala.[19] In addition, in our study, dolutegravir pharmacokinetic parameters at the postpartum visit were comparable to those found in non-pregnant HIV-positive patients on 50mg QD reported by van Lunzen *et al.* (GM (coefficient of variation (CV), %) $AUC_{0\text{-}24h}$ 48.1 (40) mg*h/L, C_{max} 3.40 (27) mg/L and C_{trough} 1.20 (62) mg/L).[16] The cord blood-to-maternal plasma ratio of 1.38 indicates efficient transport of dolutegravir across the placenta and is in line with previously reported median (IQR) ratio of 1.25 (0.68-1.68) by Mulligan *et* al. (n=18).*[18]*

As mentioned earlier, unbound dolutegravir plasma concentrations might better reflect the level of exposure to dolutegravir in pregnancy than total plasma concentrations, because plasma protein binding can decrease during the course of pregnancy.[9] In third trimester we observed a slight decrease in albumin levels. This could have caused the increased fraction unbound of dolutegravir that we observed in pregnancy versus postpartum. There are other pregnancy-related physiological changes that might alter the pharmacokinetics of a drug during the course of pregnancy. For example, it is suggested that pregnancy induces several metabolizing enzymes, including uridine diphosphate glucuronosyltransferases (UGT). Formation of dolutegravir's main metabolite, the inactive dolutegravir-glucuronide, is catalyzed by UGT1A1 and might be affected during pregnancy.[20-23] An exploratory assessment of dolutegravir glucuronide in our study did not show a significant difference in the molar metabolic ratio for dolutegravir glucuronide $AUC_{0\text{-}24h}$ versus total dolutegravir $AUC_{0\text{-}24h}$ in pregnancy. However, this study was not powered to detect a difference in UGT1A1-mediated

metabolism, therefore, a pregnancy-related effect cannot be excluded. An increase in UGT1A1-mediated metabolism is especially important for UGT1A1 substrates with a narrow therapeutic index. Larger studies are needed to explore the potential effect of pregnancy on UGT1A1 metabolism.

There are a few limitations to our study. First, the concurrent use of HIV and non-HIV comedication by some women might have lowered exposure to dolutegravir. Two women were on ART including ritonavir boosted darunavir. This combination causes a non-clinically significant, decrease of approximately 38% in dolutegravir trough plasma concentrations, probably through induction of UGT1A1 by ritonavir and/or darunavir.[24] As darunavir/ritonavir was used throughout the entire study period, it is unlikely that GMRs were affected. Patients who used cation-containing comedications were instructed to preserve time between intake of these drugs and intake of ART to limit influence on dolutegravir absorption. Second, within the PANNA study pharmacokinetics are studied after intake of antiretrovirals with food. Dolutegravir can be taken with or without food, however, food can increase dolutegravir exposure by up to 66%.[25]

In conclusion, the standard once-daily 50mg dolutegravir dose, taken with food, showed adequate exposure levels in the third trimester of pregnancy. These findings, coupled with the undetectable viral load in all women approaching delivery and their infants, suggest uncompromised efficacy of dolutegravir during pregnancy and support the use of dolutegravir-based ART for the benefit of HIV-positive women and to prevent of MTCT of HIV.

NOTES

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Potential conflicts of interest

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Table 1. Patient demographics and characteristics for enrolled patients at screening, third trimester and postpartum visits, including pregnancy outcomes

Patient characteristics (n=23)	**n (%) or median (range)**
Screening	
Age, y	33 (21-42)
Race/Ethnicity	
White	5 (22%)
Black or African American	17 (74%)
Hispanic or Latino	1 (4%)
Transmission route	
Vertical	4 (17%)
Horizontal	16 (70%)
Unknown	3 (13%)
Smoking	4 (17%) 3 light smoker (<10 cigarettes per day), 1 moderate smoker
ART naive before dolutegravir initiation	2 (9%)
Initiation of dolutegravir before conception	11 (48%)
Time on dolutegravir prior to conception, weeks	59 (1-97)
Initiation of dolutegravir in pregnancy	12 (55%)
1st trimester	1 (4%) of total
2nd trimester	7 (30%) of total
3rd trimester	4 (17%) of total
ART regimen, dolutegravir combined with	
ABC/3TC 600/300 mg	11 (48%)
TDF/FTC 245/200 mg	10 (43%)
DRV/r 800/100 mg QD	1 (4%)
DRV/r 600/100 mg BID + TDF 245 mg	1 (4%)
Third trimester	
Weight, kg, n=22	75 (60-131)
HIV-1 RNA viral load <50 copies/mL	21 (95%), 1 had VL of 105 copies/mL, but undetectable at delivery
CD4 count, cells/µL	483 (72-1551)
Delivery	
Gestational age, weeks	39 (34[a]-41)
Caesarean delivery	8 (36%); 2 unknown
Postpartum	
Weight, kg, n=10	70.8 (55-117)
HIV-1 RNA viral load <50 copies/mL, n=16	13 (59%)[b;] 9 unknown
CD4 count, cells/µL, n=14	510 (124-1380)
Pregnancy outcomes	
Birth weight, g, n=16	3220 (2120-4040)
Low birth weight (<2500 g)	2 (9%)
Small for gestational age[c,] n=16	1 (5%); 1 unknown
Infant HIV RNA PCR test negative, n=19	19 (100%), 3 unknown

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; ARV, antiretroviral; BID, twice daily; DRV/r, darunavir/ritonavir; ETV, etravirine; FTC, emtricitabine; HIV, human immunodeficiency virus; QD, once-daily; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PCR, polymerase chain reaction; TDF, tenofovir disoproxil fumarate.

[a] Stillbirth at 34 weeks of GA.

[b] Three patients had a detectable viral load at time of the postpartum visit: 53 copies/mL and corresponding C_{trough} was 1.27 mg/L, 68 copies/mL and corresponding C_{trough} of 1.14 mg/L and 237 copies/mL with corresponding C_{trough} of 1.44 mg/L.

[c] Small for gestational age was determined as <10th percentile of the fetal–infant growth chart by Fenton.[26]

Table 2. Comparison and summary for dolutegravir (50mg once-daily) in the third trimester of pregnancy and postpartum

Parameter	Third trimester (n=20)[a]	Postpartum (n=15)[a]	Third trimester vs postpartum GMR (90% CI)[b]
Total dolutegravir			
$AUC_{0\text{-}24h}$, h*mg/L	40.5 (32)	49.8 (40)	81 (68-97)
C_{max}, mg/L	3.1 (28)	3.6 (35)	85 (72-100)
T_{max}, h	3.0 (1.0-6.0)	3.1 (0.5-8.0)	
C_{trough}, mg/L	0.71 (72)	1.1 (61)	69 (54-88)
CL/F_{ss}, L/h	1.23 (32)	1.00 (40)	123 (103-147)
$T_{1/2}$, h	10.6 (37)	13.5 (32)	84 (74-95)
Vd/F, L	18.9 (36)	19.6 (35)	98 (80-119)
Unbound dolutegravir			
C_{max}, µg/L	12.3 (44)	9.18 (63)	134 (93-193)
fu, %	0.36 (0.27-0.46)	0.29 (0.22-0.38)	142 (101-200)
C_{min}, µg/L	2.87 (87)	3.38 (102)	86 (50-148)
fu, %	0.40 (0.28-0.70)	0.34 (0.23-0.70)	120 (84-170)
Dolutegravir-glucuronide[c]			
$AUC_{0\text{-}24h}$, h*mg/L	4.09 (63)	3.78 (42)	98 (84-115)
Metabolic ratio[d]	0.07 (0.02-0.13)	0.05 (0.02-0.13)	*P* = 0.088[e]

Abbreviations: $AUC_{0\text{-}24h}$, area under the curve; C_{0h}, predose concentration; CL/F_{ss}, apparent clearance under steady-state conditions; C_{max}, maximum concentration; C_{min}, minimum observed concentration; C_{trough}, concentration at the end of the dosing interval; CV, coefficient of variation; Fu, fraction unbound; GMR, geometric mean ratio; T_{max}, time to reach C_{max}.

[a] Data are geometric mean (coefficient of variation, %), except for T_{max} which is denoted as median (range), and fraction unbound and metabolic ratio are represented by the median (IQR).

[b] GMR is based on a total of 25 PK profiles including 8 within-patient comparisons for PK in third trimester vs postpartum.

[c] Data available for n=19 and n=14 in third trimester and postpartum (paired n=14), respectively.

[d] Median molar metabolic ratio for dolutegravir-glucuronide divided by dolutegravir $AUC_{0\text{-}24h}$ based on total plasma concentrations.

[e] Wilcoxon signed-rank test.

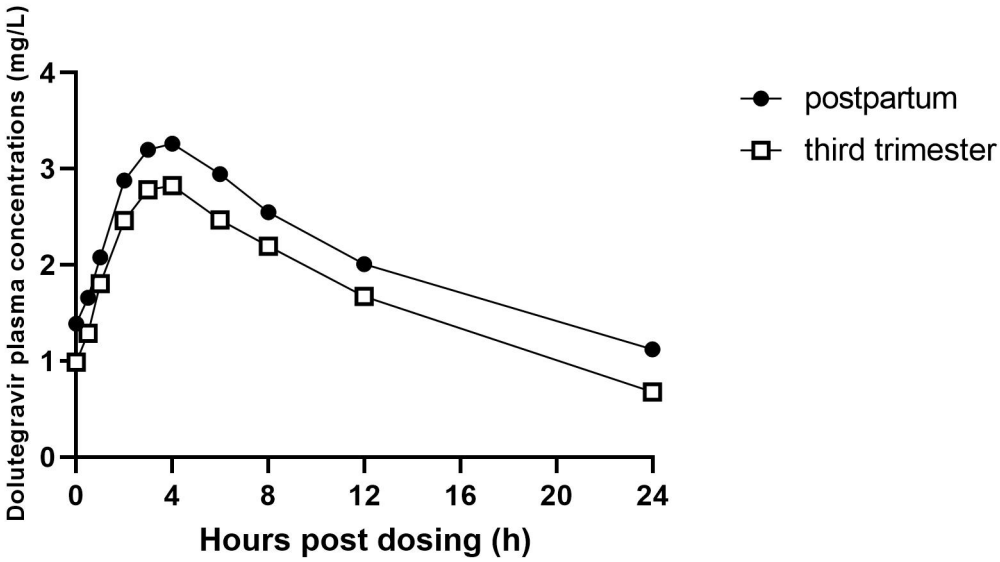

Figure 1. Geometric mean total dolutegravir concentration-time profiles during the third trimester of pregnancy and postpartum.

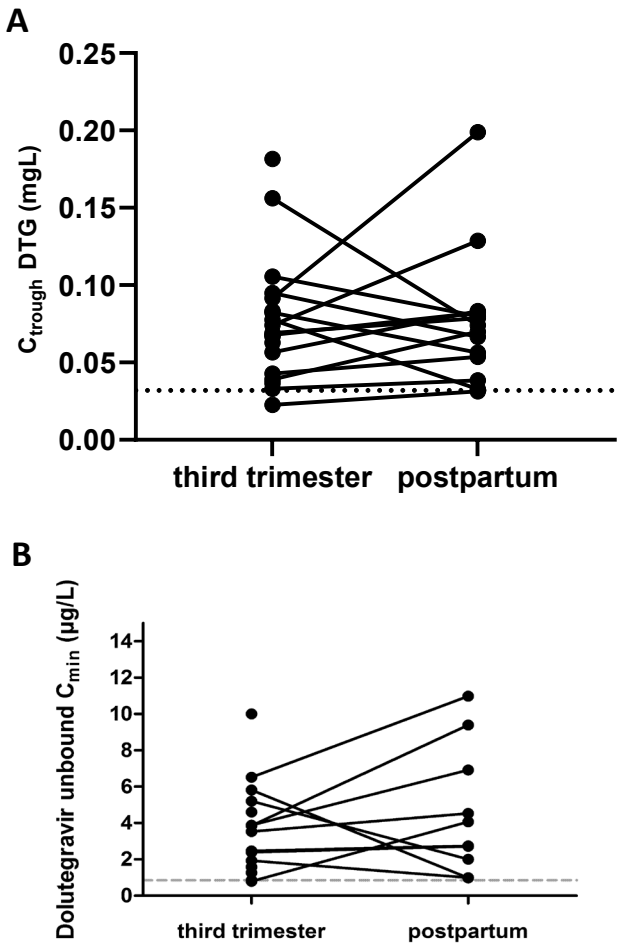

Figure 2. Individual dolutegravir total trough plasma concentrations 24 hours after intake (C_{trough}) (A) and unbound minimal plasma concentrations (C_{min}) (B) during the third trimester of pregnancy and postpartum. Grey horizontal lines indicate proposed minimal thresholds for viral inhibition for total (0.32 mg/L) and unbound plasma concentrations (0.85 µg/L).