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DOLUTEGRAVIR PLASMA CONCENTRATIONS DURING PREGNANCY AND POSTPARTUM

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1. BACKGROUND

- It is important to achieve effective blood concentrations of antiretroviral drugs to prevent treatment failure and the development of resistance. The physiological changes during pregnancy influence the pharmacokinetics of drugs. In most cases this process results in a decreased exposure during pregnancy.
- Limited data are available on dolutegravir (DTG) pharmacokinetics during pregnancy, especially on protein unbound ('free drug') concentrations, and on the placental passage of DTG. Another study (IMPAACT P1026s) reported that total DTG trough concentrations were lower during pregnancy, and median $AUC_{0\text{-}24h}$ was similar, compared to those seen postpartum.
- 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 DTG (ClinicalTrials.gov identifier NCT00825929).

Objectives

1. To describe total and unbound DTG plasma concentrations in the third trimester compared with post-partum and cord blood concentrations at delivery.
2. To describe the safety of DTG during pregnancy and monitor viral load response and pregnancy outcomes.

2. METHODS

- **Design** - Non-randomized, open-label, parallel-group, multi-center phase IV study in HIV-positive pregnant women in Europe.
- **Subjects** - Pregnant HIV-positive women on treatment with DTG 50mg once daily for at least 2 weeks, as part of their cART.
- **Pharmacokinetics** - Blood was collected at t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24h to obtain steady-state intensive 24h pharmacokinetic profiles after observed intake of DTG with food in the third trimester of pregnancy. After at least 2 weeks continuation of therapy post-partum, intensive PK sampling was repeated. When possible a cord blood sample and matching maternal blood sample were taken at delivery to estimate placental transfer. C_{max} and C_{min} samples were selected to measure free-drug concentrations.
- **Safety and efficacy** – At each visit adverse events were evaluated and HIV-1 RNA viral load was measured.
- **Bioquantification and PK analysis** - Total and unbound DTG plasma concentrations were determined with a validated UPLC method with an LLOQ of 0.0005 mg/L. Pharmacokinetic parameters were calculated using Phoenix WinNonlin (Certara®) version 8.1. Bioequivalence analysis was conducted using Phoenix.

3. RESULTS

- Nineteen HIV-positive pregnant women were enrolled in the DTG study arm. 15/17 women were included in the PK analysis, resulting in 15 third-trimester (2 not evaluable) and 10 post-partum PK profiles (6 curves not done PP, 1 not evaluable).
- Subject characteristics per trimester and pregnancy outcomes are shown in Table 1.

Pharmacokinetics

- Mean concentration-time profiles of DTG 50mg QD during third trimester and postpartum are shown in Figure 1.
- GM pharmacokinetic parameters of DTG 50mg QD in third trimester and postpartum are shown in Table 2.
- GM ratios and 90% confidence intervals (90%CI) of pharmacokinetic parameters of DTG 50mg QD in third trimester compared to postpartum are shown in Table 2.
- Individual pharmacokinetic parameters after DTG 50mg QD administration during third trimester and postpartum are shown in Figure 2.

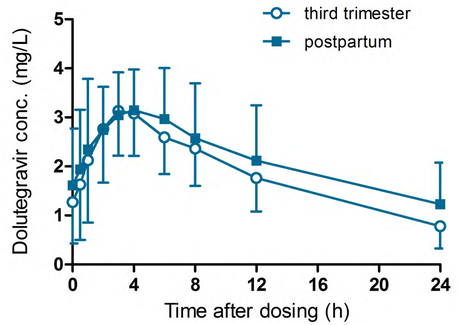
Table 1: Subject characteristics and pregnancy outcomes.

General (n=17)	
Age (years)	31 (21-42)
Black; white; other [n (%)]	13 (76%); 3 (18%); 1 (6%)
Treatment naive at conception [n (%)]	2 (12%)
Conception on DTG [n (%)]	8 (50%), of n=16, one start date DTG unkown
Concomitant ARVs [n (%)]	ABC/3TC 8 (47%); TDF/FTC 7 (41%); DRV/r 800/100mg QD 1 (6%); DRV/r 600/100mg BID, TDF 1 (6%)
Third trimester (n=15 evaluable)	
Gestational age (weeks)	33.4 (30.9-38.1)
Weight (kg)	72.5 (60-131)
HIV RNA undetectable <50 cps/mL [n (%)] n=17	17 (100%)
CD4 count (cells/uL), n=17	505 (194-1551)
Postpartum (n=10)	
Time after delivery (weeks)	6.0 (2.9-7.4)
Weight (kg)	70.5 (55-117)
HIV RNA undetectable <50 cps/mL [n (%)]	10 (90%); 1 positive 53 copies/mL#; 5 unknown
CD4 count (cells/uL)	588 (283-1380)
Pregnancy outcomes (n=17)	
Gestational age (weeks)	40 (37-42)
Caesarian section [n(%)]	7/15 (47%); 2 unknown
Infant birth weight (grams)	3170 (2120-4040), 1 unknown
Low body weight (<2500 g) [n(%)]	2/16 (13%), 1 unknown
Small for gestational age [n(%)]	1/16 (6%), 1 unknown*
Infant HIV DNA PCR negative [n(%)]	14/14 (100%); 3 unknown

Median (range); or number (percentage)
ARVs: antiretrovirals, ABC=abacavir; 3TC=lamivudine; TDF=tenofovir disoproxil fumarate; FTC=emtricitabine; DRV/r = darunavir/ritonavir; qd=once daily; BID=twice daily
 # C_{trough} was 1.27 mg/L (postpartum)
** SGA small for gestational age, based on Fenton graph, 2003*

3. RESULTS (continued)

Figure 1: Mean (±SD) concentration-time profile after administration of DTG 50mg QD during third trimester and postpartum.



- 2/15 patients had a subtherapeutic C_{trough} (<0.32 mg/L (EC_{90})) in the third trimester; C_{trough} was 0.11 mg/L and 0.28 mg/L. None of the subjects had a subtherapeutic C_{trough} postpartum.
- The median (range, n=10) ratio of cord blood/maternal plasma DTG concentrations was 1.38 (0.63-1.81).

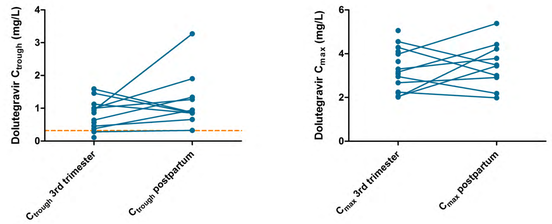
Table 2: Total DTG 50mg QD geometric mean (%CV) pharmacokinetic parameters in third trimester and postpartum and geometric mean ratios (90% CI).

PK parameter	Third trimester (n=15)	Postpartum (n=10)	GM Ratio* (%) [90% CI]
$AUC_{0\text{-}24h}$ (h*mg/L)	40.8 (35)	47.0 (42)	86 (68-110)
C_{max} (mg/L)	3.15 (31)	3.34 (32)	93 (77-113)
C_{max} unbound (mg/L)	0.012 (44)	0.009 (63)	134 (93-193)
Fraction unbound (%)	0.36 (0.27-0.46)	0.29 (0.22-0.38)	142 (101-200)
T_{max} (h)	3.0 (1.0-4.5)	3.8 (0.5-8.0)	
C_{0h} (mg/L)	1.00 (90)	1.22 (105)	79 (48-132)
C_{trough} (mg/L)	0.68 (84)	1.03 (68)	71 (49-102)
C_{min} (mg/L)	0.66 (90)	0.92 (84)	74 (49-112)
C_{min} unbound (mg/L)	0.003 (87)	0.003 (102)	86 (50-148)
Fraction unbound (%)	0.40 (0.28-0.70)	0.34 (0.23-0.70)	120 (84-170)
CL/F (L/h)	1.23 (35)	1.06 (42)	116 (91-147)

** Third trimester vs postpartum. T_{max}: median (min-max); fraction unbound: median (IQR).*

3. RESULTS (continued)

Figure 2: DTG 50mg QD individual C_{trough} and C_{max} in third trimester and postpartum.



Orange line represents suggested minimal therapeutic concentration of 0.32 mg/L.

Safety

- Maternal safety - Two SAE (not drug related) were reported; two hospital admissions due to suspected pre-eclampsia/HELLP-syndrome (in one case ruled out and for one confirmed)
- Fetal safety - One intrauterine fetal death (34 weeks of pregnancy) was reported due to cholestasis of pregnancy syndrome and was considered unlikely to be drug related by the treating physician. One case of hypospadia was reported, considered unrelated to DTG use.
- No children were HIV-infected (3 unknown due to loss to follow-up).

4. CONCLUSIONS

- Although variability is high, DTG $AUC_{0\text{-}24h}$ seems similar in late pregnancy and postpartum.
- DTG total trough plasma concentrations seem lower in the 3rd trimester compared to postpartum. However, unbound dolutegravir plasma C_{min} are unchanged in the 3rd trimester as compared to postpartum.
- In this study the DTG free fraction in pregnant women in the 3rd trimester seems higher than postpartum (42% for C_{max} and 20% for C_{min}).
- These findings, coupled with the undetectable viral loads at delivery, suggest uncompromised efficacy of dolutegravir 50mg QD in pregnancy.

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