Dolutegravir Pharmacokinetics in HIV-Infected Pregnant and Postpartum Women

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P438

Introduction

- Antiretroviral therapy (ART) can reduce the risk of perinatal transmission to < 1% and is recommended for all pregnant women.
- Dolutegravir (DTG) is an integrase strand transfer inhibitor (INSTI) recommended for INSTI-naïve and some INSTI-experienced patients with human immunodeficiency virus type 1 (HIV-1).
- The recommended DTG dose (for non-pregnant adults) is 50 mg once-daily (without co-administration of potent UGT1A/CYP3A inducers such as efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir or rifampin).[1]
- During pregnancy, physiological changes cause decreased exposure to many antiretrovirals. No data are available on the pharmacokinetic behavior of dolutegravir (DTG) during pregnancy, nor on infant washout pharmacokinetics.
- The IMPAACT P1026s protocol describes the pharmacokinetics of antiretroviral agents in HIV-infected pregnant women in comparison to post-partum kinetics (www.impaactgroup.org), including a DTG arm.

Methods

- The IMPAACT P1026s study (ClinicalTrials.gov identifier NCT00042289) is an ongoing nonrandomized, open-label, parallel-group, multi-center phase-IV prospective study of antiretroviral pharmacokinetics and safety in HIV-infected pregnant women that includes an arm for receiving dolutegravir.
- Samples were collected at 20-28 weeks gestation, 30-38 weeks gestation and between 3 to 12 weeks following delivery. Serial blood collection was drawn at pre-dose, 1, 2, 4, 6, 8,12 and 24 hours post-dose.
- Infant washout samples were collected, if birth weight was > 1,000 grams and there were no severe malformations or medical conditions, at 2-10 hours, 18-28 hours, 36-72 hours and 5-9 days post delivery.
- DTG was measured using validated LC/MS/MS (quantitation limit: 0.005 mcg/mL).
- PK parameters were calculated with standard non-compartmental methods. Two-tailed Wilcoxon signed rank tests compared within-subject PK parameters with a two-sided p-value < 0.10.

References

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Results

Maternal Pharmacokinetics

- Data were available for 2nd trimester (n = 9), 3rd trimester (n = 15), postpartum (n = 9) and infant washout (n = 10). [Table 1]
- DTG AUC was 25 – 30% lower in the 2nd and 3rd trimester compared to paired postpartum data; differences were not significant (n=4 and 7 for 2nd and 3rd trimester comparisons to postpartum). [Table 2, Figure 1]
- DTG C_{max} was significantly lower in the 3rd trimester compared to paired postpartum data. C_{24} were 41% lower in both 2nd and 3rd trimester, but differences were not significant. [Table 2, Figure 2]
- 6/9 (67%) subjects in the 2nd trimester, 12/15 (80%) subjects in the 3rd trimester and 8/9 (89%) subjects postpartum had an AUC above the 10th percentile (37.5 mcg*hr/mL) of non-pregnant adults.

Figure 1. Median Dolutegravir Concentrations

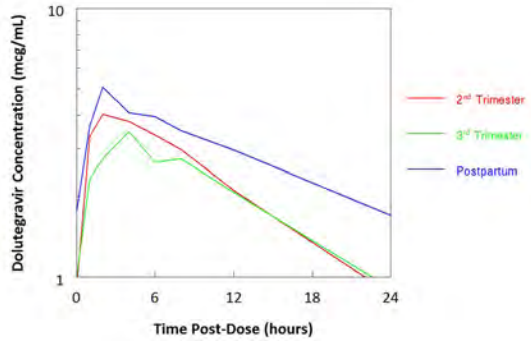


Figure 2. Dolutegravir C_{24} Ante- and Postpartum

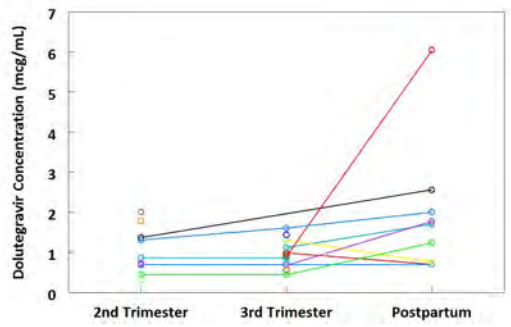
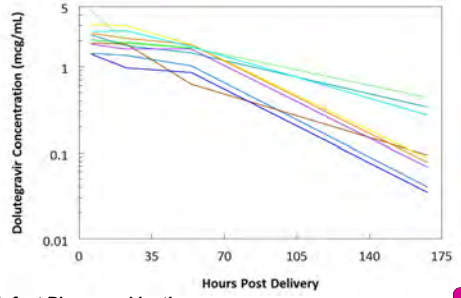


Figure 3. Infant Dolutegravir Concentrations



Infant Pharmacokinetics

- Washout pharmacokinetic data were available for 10 infants; elimination half-life was 35 hours. [Table 3, Figure 3]

Maternal and Infant Safety

- One maternal AE was possibly treatment related: moderately increased ALT. Two additional maternal SAEs were reported: pre-eclampsia and atypical pre-eclampsia.
- Four infants had congenial anomalies: total anomalous pulmonary venous return; polycystic right kidney and cystic fibrosis; congenital chin tremor; filum terminale fibrolipoma and sacral dimple. Four infants had hypoglycemia.

Table 3. Infant Washout of Dolutegravir (n = 10)

Parameter	Median (IQR)
C_{max} (mcg/mL)	1.96 (1.42 - 2.48)
T_{max} (hr)	6.9 (3.3 - 8.6)
$T_{1/2}$ (hr)	34.5 (28.6 - 39.9)

Demographics

Table 1. Clinical Characteristics (n = 21)

Maternal Demographics	N (%) or Median (Range)
Age at Delivery (years)	31.8 (21.6 – 42.3)
Weight at Delivery (kg)	88 (61.8 – 126)
Race/Ethnicity White; Black; Hispanic; Asian/Pac. Islander; American Indian/Alaskan	3 (14%); 14 (66%); 2 (10%); 1 (5%); 1 (5%)
Concomitant ARVs ABC; 3TC; FTC; TDF; ZDV MVC; T20; DRV/RTV	15 (71%); 15 (71%); 5 (24%); 4 (19%); 1 (5%) 1 (5%); 1 (5%); 1 (5%)
Country: United States	21 (100%)
2nd Trimester	
Gestational Age	23.4 (21.4 – 25.2)
HIV-1 RNA ≤ 50 copies/mL	9 (100%)
CD4 (cells/mm^3)	627 (353 – 1175)
3rd Trimester	
Gestational Age	33.6 (30.7 – 37.4)
HIV-1 RNA ≤ 50 copies/mL	15 (100%)
CD4 (cells/mm^3)	468 (78 – 993)
Postpartum	
Weeks After Delivery	7.3 (6 – 12)
HIV-1 RNA ≤ 50 copies/mL	8 (89%)
CD4 (cells/mm^3)	646 (357 – 1142)
Pregnancy Outcomes	
Gestational Age (weeks)	38.9 (36.3 – 42.3)
Birth Weight (grams)	3116 (2355 – 3670)
Infection Status: Uninfected / Pending	9 (50%) / 9 (50%)

Table 2. Maternal Dolutegravir Pharmacokinetic Parameters

Parameter Median (IQR)	2nd Trimester n = 9	3rd Trimester n = 15	Postpartum n = 9	Historical Control[1]
AUC_{0-24} (mcg*hr/mL)	58.4 (47.6 - 64.5)	48.7 (40.3 - 57.6)	71.1 (58.0 - 83.1)	53.6 (27)
C_0 (mcg/mL)	0.88 (0.64 - 1.98)	1.01 (0.75 - 1.42)	1.76 (0.99 - 2.29)	-
C_{max} (mcg/mL)	4.59 (3.89 - 5.22)	3.92 (3.36 - 4.44)	5.10 (3.75 - 7.23)	3.67 (20)
T_{max} (hr)	2 (2 - 4)	4 (2 - 4)	2 (2 - 4)	2 to 3
C_{24} (mcg/mL)	0.86 (0.69 - 1.37)	0.91 (0.74 - 1.21)	1.70 (0.76 - 2.00)	-
C_{min} (mcg/mL)	0.86 (0.64 - 1.37)	0.86 (0.55 - 1.13)	1.70 (0.70 - 2.00)	1.11 (46)
CL/F (L/hr)	0.86 (0.78 - 1.05)	1.03 (0.87 - 1.24)	0.70 (0.60 - 0.86)	1
$T_{1/2}$ (hr)	10.5 (8.7 - 12.6)	11.2 (10.3 - 13.0)	12.3 (10.5 - 15.6)	14

[1]Historical data from Tivicay™ (Dolutegravir) package insert, represented as geometric mean (%CV)

Discussion and Conclusion

- AUC and trough DTG exposure appear to be lower in pregnancy compared to postpartum, but antepartum AUC and trough values are still similar to those seen in non-pregnant adults.
- During pregnancy, UGT1A1 activity is induced by increased progesterone levels.[2] CYP3A4 induction has also been observed during pregnancy, resulting in lowered concentrations of CYP3A4 substrates such as protease inhibitors.[3] DTG is metabolized primarily by UGT1A1, with some contribution of CYP3A4.
- DTG's elimination half-life in infants was over twice that observed in historical controls of non-pregnant adults as well as this study's participants both ante and postpartum. More pharmacokinetic data in pregnant women and safety data in infants are needed before dolutegravir can be recommended for clinical use during pregnancy.

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