Pharmacokinetics of Tenofovir Alafenamide 25mg with PK Boosters During Pregnancy & Postpartum

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Disclosures

- None
- The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH

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Background

- Tenofovir alafenamide fumarate (TAF) is a common component of multiple ARV regimens
- Physiologic changes associated with pregnancy can alter the drug disposition of antiretroviral (ARV) medications
- TAF is **not** currently recommended during pregnancy due to insufficient data describing its use in this population[1]
- TAF exposures during pregnancy and postpartum with 25 mg alone and 10 mg with cobicistat are comparable to measures in non-pregnant adults living with HIV[2]

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[1]Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.
[2]Momper JD, et al. 22nd International AIDS Conference. 2018.

Objective

- To characterize the PK of TAF 25 mg with PK boosters (i.e., RTV or COBI) during pregnancy and PP among women living with HIV

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Study Design

- IMPAACT 1026s is an international open-label, multicenter study examining the PK of ARV medications prescribed in pregnant women living with HIV
- ARV medications are prescribed as clinical care and treatment management/toxicities are handled by the participant's primary care provider
- Pregnant women receiving TAF 25 mg with PK boosting (i.e., COBI or RTV) were eligible for this arm
  - Enrollment could occur during 2nd trimester (2T) or 3rd trimester (3T)
  - On stable TAF dosing for ≥2 weeks prior to first PK assessment

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Methods

- Steady-state intensive PK assessments were performed during 2T/3T and 6-12 weeks postpartum (PP) following observed dosing of ARV medications
- TAF plasma concentrations were quantified using a validated LC-MS/MS method
- Individual PK parameters were calculated using post-hoc Bayesian estimation in NONMEM
- Geometric mean ratios (GMR) with 90% confidence intervals (CI) were calculated within-participant between 2T vs. PP and 3T vs. PP
- Paired comparisons were made using a two-sided Wilcoxon signed-rank test (α=0.10)
- Protocol-defined comparisons to 10th percentile TAF AUCs in non-pregnant adults were also performed

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Participant Demographics

- Total of 17 women enrolled (all from the United States): 59% black, 41% Hispanic

Characteristic	2T (n=7)	3T (n=15)	PP (n=13)
Age (yr), mean (SD)	30.8 (7.5)	29.5 (7.2)	31.3 (6.6)
Weight (kg), mean (SD)	105.7 (26.1)	97.4 (23.2)	97.6 (34.2)
Gestational age or time after delivery (wk), mean (SD)	23.4 (2.4)[a]	33.0 (2.3)[a]	9.1 (2.0)[b]
Duration of TAF therapy (wk), median (range)	12 (6 – 86)	26 (5 – 100)	40 (15 – 114)
Viral Load (copies/mL), median (range)	<40 (<40 - 511)	<40 (<40 – 120)	<40 (<40 - 396)
HIV-1 RNA ≤50 copies/mL, n(%) ≤400 copies/mL, n(%)	 4/6 (66.7%) 5/6 (83.3%)	 12/13 (92.3%) 13/13 (100%)	 7/8 (87.5%) 8/8 (100%)
Concomitant PI/booster Darunavir/cobicistat (DRV/c) Darunavir/ritonavir (DRV/r) Atazanavir/cobicistat (ATV/c) Atazanavir/ritonavir (ATV/r)	 4/6 (66%) 0/6 (0%) 1/6 (17%) 1/6 (17%)	 7/14 (50%) 3/14 (22%) 2/14 (14%) 2/14 (14%)	 2/8 (25%) 2/8 (25%) 2/8 (25%) 2/8 (25%)

[a]Gestational age [b]Time after delivery

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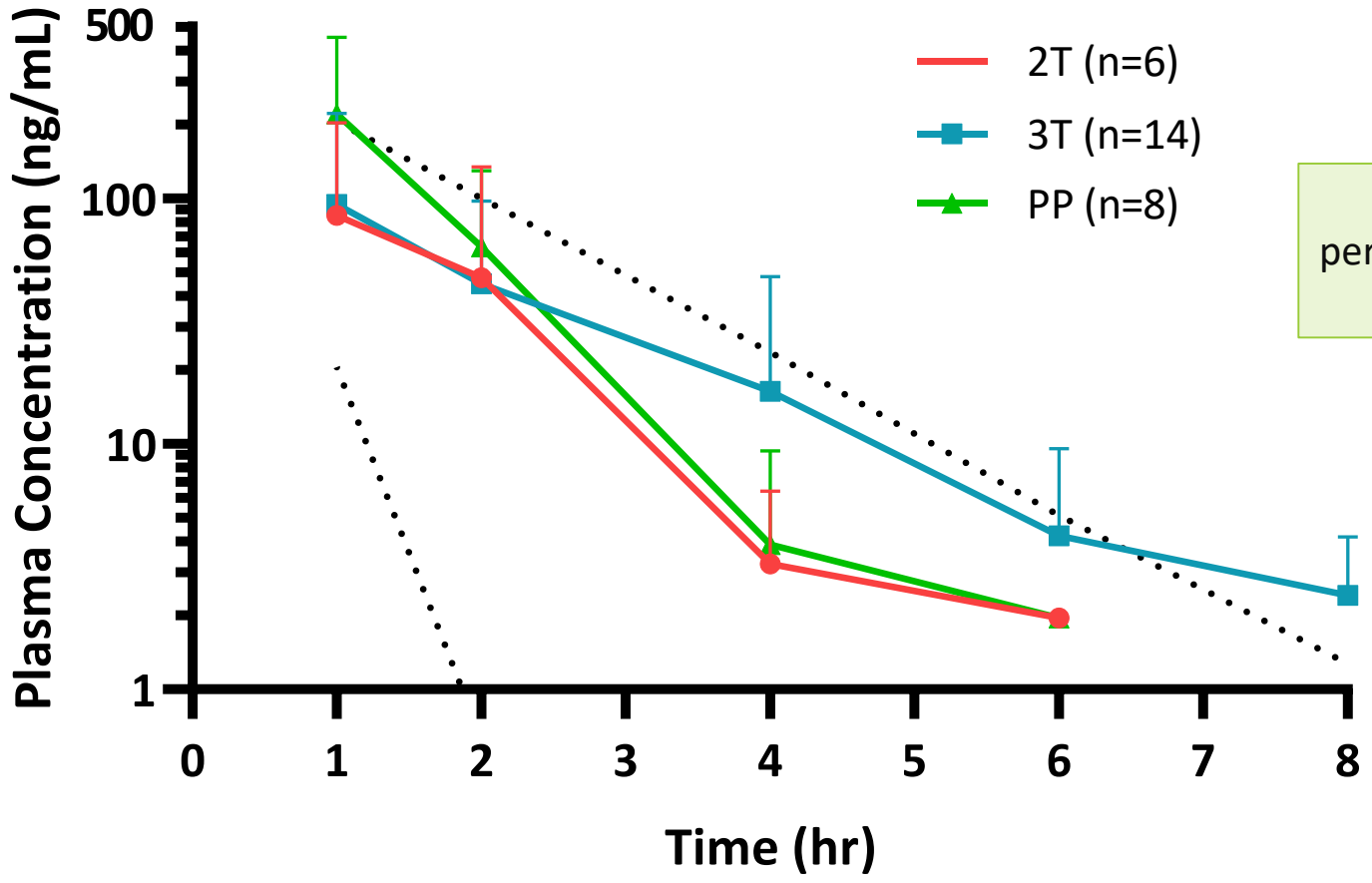
TAF Plasma Concentration vs. Time Profiles



Data presented as mean (%CV)

Dashed lines indicate 5th and 95th percentile values from non-pregnant adults living with HIV on E/C/F/TAF 10 mg

All samples were BLQ (=3.9 ng/mL) at pre-dose, 12 and 24 hrs post-dose

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Pregnancy vs. Postpartum PK Comparisons

PK Parameter	2nd Trimester (n=6)	3rd Trimester (n=14)	Postpartum (n=8)	3T vs. PP (n=8)	
				GMR (90% CI)	P-value
$AUC_{0-\tau}$ (ng·h/mL)	133 (128 – 720)	335 (192 – 549)	507 (221 – 693)	-6% (-62%, 133%)	0.74
C_{max} (ng/mL)	44 (41 – 219)	101 (78 – 119)	164 (107 – 337)	-38% (-65%, 10%)	0.15
CL/F (L/hr)	188 (35 – 195)	75 (46 – 130)	49 (37 – 123)	6% (-57%, 161%)	0.64
V/F (L)	55 (21 – 55)	55 (36 – 66)	45 (25 – 58)	-13% (-63%, 108%)	0.69
$T_{1/2}$ (hr)	0.20 (0.20 – 0.33)	0.32 (0.26 – 0.61)	0.31 (0.25 – 0.66)	3% (-34%, 61%)	0.94

Summary PK statistics reported as median (IQR)

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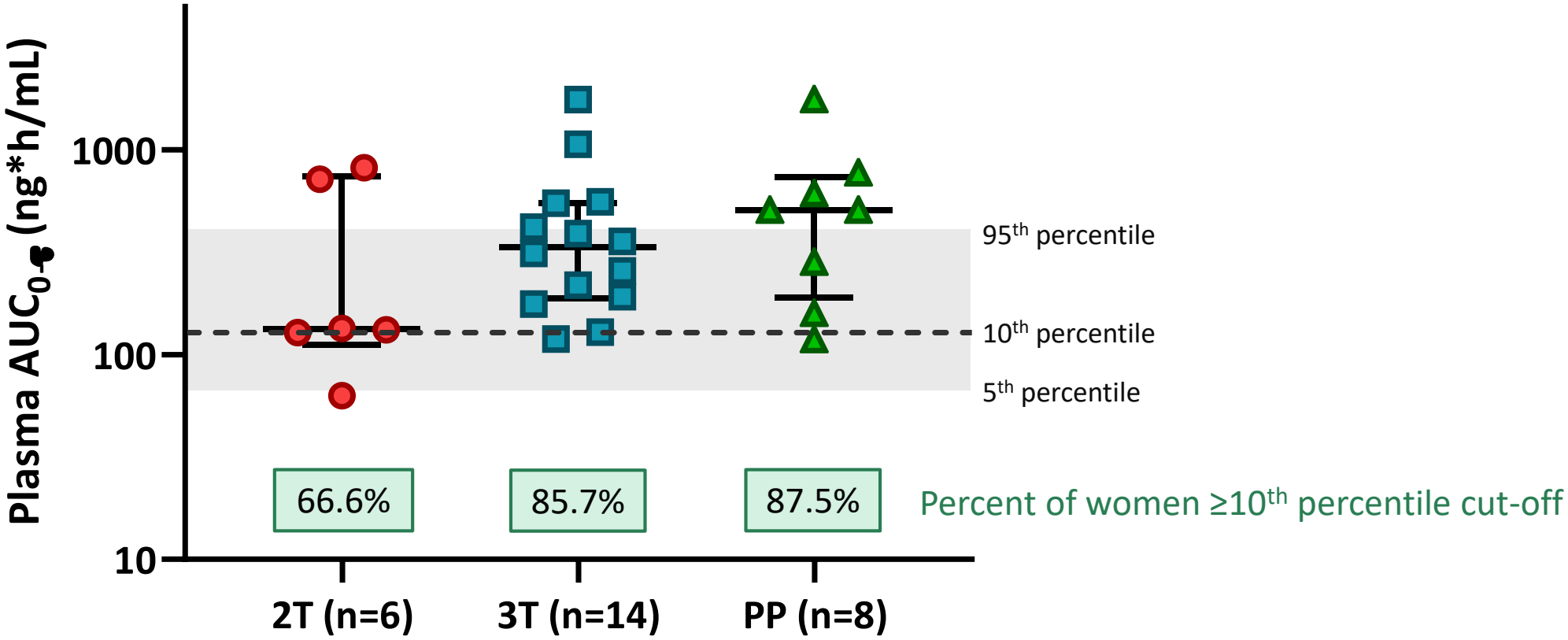
TAF AUC during Pregnancy vs. Postpartum



Data presented as median (IQR)
Shading indicates AUC percentile data from non-pregnant adults living with HIV on E/C/F/TAF 10 mg

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Birth & Safety Outcomes

Maternal VL at delivery:

16/17 (94.1%) with VL ≤50 copies/mL

17/17 (100%) with VL ≤400 copies/mL

Characteristic	N=15[a]
Birth weight (g), mean (SD)	3223 (558)
Gestational age at delivery (wk), median (range)	38.1 (29.6 – 40.6)
Most Definitive HIV Status, n(%)	
Uninfected	6 (40%)
Indeterminate[b]	7 (47%)
Pending	2 (13%)
Congenital anomalies[c]	
Sacral dimple	1
Mongolian spot	1
Microcephalia	1

[a]One mother withdrew infant consent, 1 intrauterine fetal demise
[b]All tests were negative, but unable to confirm "uninfected" status from follow-up testing due to study exit
[c]All not related to study drug

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Conclusions

- Plasma TAF 25 mg exposures with PK boosters did not significantly differ between 3T and PP, though CIs were wide due to small sample sizes
- Additional PK data from pregnant women during 2T are needed
- TAF 25 mg with boosting appeared safe and well-tolerated by mothers and infants in this small sample size
- Analysis of maternal delivery, cord blood and infant washout samples are pending
- Data on the long-term safety, efficacy and intracellular PK of TAF during pregnancy are needed to optimize its use in this population

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