Population PK Analyses Predict CAB LA Dose Adjustments Are Not Required for Pregnant Women

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Introduction

- Long-acting cabotegravir (CAB LA) dosed every 2 months is approved for use as pre-exposure prophylaxis (PrEP)[1]
- Pregnancy can alter drug clearance and protein binding, affecting total and unbound drug concentrations[2]
  - CAB LA for PrEP has been administered to pregnant participants in the HPTN 084 Open Label Extension (OLE)[3]
  - A pregnancy population PK (PPK) model was developed using a subset of participants (n=75) from the HPTN 084 OLE
  - An exploratory analysis of unbound CAB concentrations was performed to support dosing recommendations for CAB LA use during pregnancy

Methods

- An established CAB PPK model[4] was adapted to describe total CAB concentrations in 75 women from HPTN 084 who continued CAB LA for PrEP during pregnancy
  - Criteria for inclusion in the PK subpopulation were described previously[5]
  - Total CAB concentrations were generated for samples from pre-pregnancy through postpartum, whereas unbound CAB concentrations were generated using the samples from the same pre-pregnancy to delivery visits but was not determined for post-partum visits. Lower limits of quantification were 0.025 µg/mL for total CAB and 0.05 ng/mL for unbound CAB
  - Previous model parameters were fixed, and clearance (CL/F) and absorption rate constant (KA2) were estimated
  - Pregnancy as a covariate was tested as a continuous covariate on CL/F and KA2
  - The final CAB pregnancy PPK model was used to simulate total plasma concentration-time profiles during pregnancy using conservative approaches
    - Continuation simulations assumed CAB steady state was achieved before pregnancy and exposures were estimated for the end of each trimester (TM) to best simulate pregnancy effect
    - Simulations were also performed to explore CAB LA initiation during each TM
  - Individual fraction unbound (fu) observed during each TM, as well as predicted total CAB concentrations for these periods, were used to derive predicted unbound CAB trough (C_τ) values, which were compared with the in vitro CAB concentration needed to inhibit HIV viral activity by 90%. (IC_{90}; 0.407 ng/mL)[6]

Results

- Demographics of participants included in the pregnancy PPK population are shown in Table 1

Table 1. Summary of Demographics

Demographic	Summary (n=75)	
	Mean (SD)	Median (range)
Baseline age, year	25 (4.4)	25 (16, 35)
Baseline body weight, kg	68 (15.4)	65 (43, 123)
Baseline BMI, kg/m^2	27 (5.8)	26 (18, 48)
Baseline serum creatinine, µmol/L	52 (8.1)	51 (35, 68)
Baseline serum albumin, g/L	43.8 (3.0)	44 (34, 53)

BMI, body mass index; SD, standard deviation.

- Data included in the analyses are described in Table 2

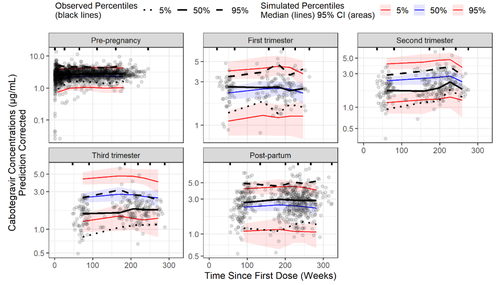
Table 2. Summary of Data Included in the Analyses

Pregnancy stage, n (%)	Number of participants with observations (n=75)	Number of total CAB plasma concentrations (N=2679)	Number of unbound CAB plasma concentrations (N=845)	Number of CAB fu values (N=842)
Pre-pregnancy	75 (100)	1497 (56)	187 (22)	185 (22)
TM1	75 (100)	176 (7)	176 (21)	175 (21)
TM2	75 (100)	257 (10)	257 (30)	257 (31)
TM3	75 (100)	226 (8)	225 (27)	225 (27)
0 to <2 weeks postpartum	46 (61)	52 (2)	—	—
2 to <3 weeks postpartum	50 (67)	50 (2)	—	—
3 to <6 weeks postpartum	71 (95)	76 (3)	—	—
6 to <12 weeks postpartum	67 (89)	66 (3)	—	—
≥12 weeks postpartum	74 (99)	279 (10)	—	—

fu, fraction unbound; n, number of participants; N, number of observations.

Changes in CAB plasma protein binding offset increased CAB clearance in pregnancy. Given that unbound CAB concentrations are predicted to remain at levels that inhibit HIV replication, CAB LA for PrEP can be continued or initiated during pregnancy at the standard dosing regimen.

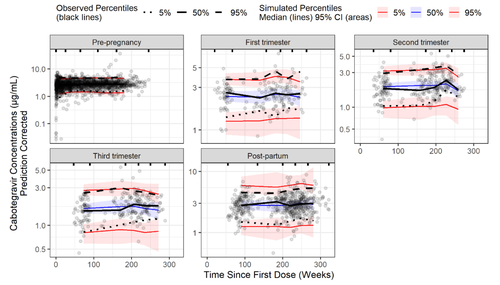
Figure 1. pcVPCs Assessing the Predictive Performance of the Previously Developed CAB Adult PPK Model for the Pregnancy Dataset



CI, confidence interval; PPK, population pharmacokinetic; pcVPC, prediction-corrected visual predictive check. Open circles represent observed total CAB concentrations. Solid black lines represent the median of observed data, and dotted and dashed lines represent the 5th and 95th percentiles of the observed data, respectively. Blue solid lines represent the median of simulated data and red solid lines represent the 5th and 95th percentiles of the simulated data. Blue and pink shaded areas represent the 95% CI of the median and 5th and 95th percentiles of the simulated data, respectively.

- The final model can accurately predict the observed data in all stages of pregnancy (Figure 2)
- CL/F increased linearly during pregnancy (0.401%/day) from 0.125 L/h to 0.167 L/h (33.7% increase), 0.22 L/h (75.8% increase), and 0.265 L/h (112% increase) at the end of TM1, TM2, and TM3, respectively; pre-pregnancy CL/F was re-established by 8 weeks postpartum
- Pregnancy-related covariates on KA2 were not retained in the model due to increased model instability without successful minimization and with limited improvement in model fits

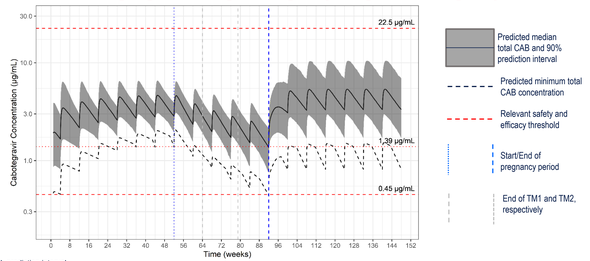
Figure 2. pcVPCs of the Final CAB Pregnancy PPK Model Stratified by Pregnancy Trimester and Before and After Pregnancy



CI, confidence interval; pcVPC, prediction-corrected visual predictive check; PPK, population pharmacokinetic. Open circles represent observed total CAB concentrations. Solid black lines represent the median of observed data and dotted and dashed lines represent the 5th and 95th percentiles of the observed data, respectively. Blue solid lines represent the median of the simulated data and red solid lines represent the 5th and 95th percentiles of the simulated data. Blue and pink shaded areas represent 95% CI of the median and 5th and 95th percentiles of the simulated data, respectively.

- Using conservative simulation criteria, pregnancy reduced total CAB exposures relative to the pre-pregnancy period (Figure 3, Table 3)

Figure 3. Simulated Median (90% PI) Total CAB Concentration-Time Following the Standard CAB LA PrEP Dosing Regimen Throughout Pregnancy Using the Final Pregnancy Model



PI, prediction interval.

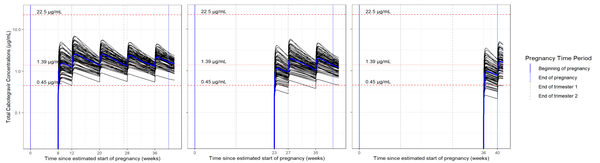
Table 3. Summary of Estimated Total CAB Parameters by Pregnancy Period Compared With Pre-pregnancy Values

Parameter, geometric mean (10th-90th percentile)	Predicted total CAB parameter				Comparison to pre-pregnancy		
	Pre-pregnancy	TM1	TM2	TM3	TM1	TM2	TM3
AUC(0-τ,ss), µg·h/mL	5044 (4071-5947)	4187 (3176-5177)	3072 (2272-4084)	2500 (1823-3402)	83.0 (78.0-87.1)	60.9 (55.8-68.7)	49.6 (44.8-57.2)
Cmax(ss), µg/mL	4.63 (3.41-6.11)	4.15 (3.09-5.62)	3.03 (2.09-4.30)	2.47 (1.74-3.58)	89.6 (90.6-92.0)	65.4 (61.3-70.4)	53.3 (51.0-58.6)
Cτ(ss), µg/mL	2.79 (2.18-3.47)	2.07 (1.53-2.58)	1.55 (1.16-2.00)	1.28 (0.919-1.68)	74.2 (70.2-74.4)	55.6 (53.2-57.6)	45.9 (42.2-48.4)

AUC(0-τ,ss), area under the total CAB-concentration-time curve from time zero to the end of dosing interval at steady state; Cmax (ss), maximum total CAB plasma concentration at steady state; C_τ (ss), CAB trough at steady state. Steady state achieved before pregnancy. Exposures represent the end of each period.

- Simulations show accumulation of total CAB concentration-time after initiation during pregnancy (Figure 4)

Figure 4. Predicted Total CAB Concentration-Time After Initiation of the Standard PrEP Dosing Regimen in TM1 (Left Panel), TM2 (Center Panel), and TM3 (Right Panel)



IM, intramuscular; Q4W, every 4 weeks. Black curves represent individual profiles upon receiving 600 mg Q4W LA IM dosing. The blue curve represents the median profile. Red lines indicate concentrations matching with the indicated efficacy and safety threshold. Vertical blue and gray lines indicate pregnancy-related time points as defined in the legend.

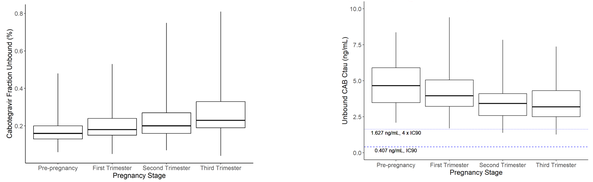
- Estimated unbound CAB C_τ remained >4x the protocol-defined target (0.664 µg/mL) IC_{90} in >90% of women throughout pregnancy when continuing CAB LA (Figure 5, right panel) and >IC_{90} after initiation during pregnancy (Table 4)
- Unbound concentrations increase with repeat dosing after initiation during pregnancy (Figure 6)

Table 4. Summary[a] of Estimated Unbound CAB C_τ Values by Pregnancy Period After Continuation and Initiation During Pregnancy

Scenario	Unbound CAB, µg/mL				Fold > IC_{90}[b]		
	Pre-pregnancy	TM1	TM2	TM3	TM1	TM2	TM3
Continuation during pregnancy[c,d]	4.59 (3.18, 6.88)	3.90 (2.62, 5.80)	3.29 (2.15, 5.02)	3.17 (1.85, 5.23)	9.58 (6.44, 14.3)	8.08 (5.28, 12.3)	7.79 (4.55, 12.9)
Initiation end TM1, continue PrEP[e]	—	2.27 (1.18, 4.07)	2.76 (1.67, 4.19)	3.00 (1.91, 4.69)	5.58 (2.90, 10.0)	6.78 (4.10, 10.3)	7.37 (4.69, 11.5)
Initiation end TM2, continue PrEP[f]	—	—	1.90 (1.08, 3.47)	2.51 (1.49, 3.89)	—	4.67 (2.65, 8.53)	6.17 (3.66, 9.56)
Initiation end TM3	—	—	—	1.82 (0.94, 3.15)	—	—	4.47 (2.30, 7.74)

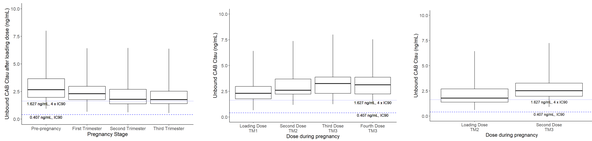
[a]Shown as geometric mean (10th, 90th percentiles). [b]IC_{90} = 0.407 ng/mL. [c]Initiation doses administered before pregnancy result in geometric mean (10th, 90th percentile) unbound CAB C_τ of 2.72 ng/mL (1.47, 5.17). [d]Steady state achieved before pregnancy. [e]Data represent C_τ after initiation doses administered 4 weeks before TM1 end and 8 weeks after TM2 injection 2 and TM3 injection 4. [f]Data represent C_τ after initiation doses administered 4 weeks before TM2 end and 8 weeks after TM3 injection 2.

Figure 5. Change in CAB Fu During Pregnancy (Left Panel) and Distribution of Estimated Unbound CAB C_τ After Continuation of the Standard Regimen (Right Panel)



fu, fraction unbound; IC_{90}, CAB concentration needed to inhibit HIV viral activity by 90%. Horizontal lines in middle of boxes represent median values. Upper and lower edges of boxes represent 25th and 75th percentiles. Vertical bars represent minimum and maximum values.

Figure 6. Distribution of Estimated Unbound CAB C_τ Values for the Initiation Injections by Pregnancy Period (Left Panel) and After Each Injection of the Standard Regimen When CAB LA Is Initiated at the End of TM1 (Center Panel) or TM2 (Right Panel)



C_τ, CAB trough. Horizontal lines in middle of boxes represent median values. Upper and lower box edges represent 25th and 75th percentiles (interquartile range, IQR). Vertical bars represent minimum and maximum values. Blue dashed line represents CAB IC_{90}. Blue dotted horizontal line represents 4x IC_{90} (1.627 ng/mL).

Conclusions

- Given the unbound CAB concentrations are predicted to remain at levels that inhibit HIV replication, CAB LA for PrEP may be continued or initiated during pregnancy at the standard dosing schedule

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References: 1. Apretude [prescribing information]. Durham, NC: ViiV Healthcare; 2025. **2.** Feghali et al. *Semin Perinatol.* 2015;39:512-519. **3.** Marzinke et al. CROI 2026; Denver, CO. Poster 789. **4.** Han et al. *Br J Clin Pharmacol.* 2022;88:4607-4622. **5.** Marzinke et al. AIDS 2024; Munich, Germany. Oral presentation. **6.** Johns et al. *J Med Chem.* 2013;56:5901-5916.

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