Assessment of Total and Unbound Cabotegravir Pharmacokinetics Among Pregnant Women in HPTN 084

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BACKGROUND

HPTN 084 found that long-acting cabotegravir (CAB-LA) significantly reduced the risk of HIV acquisition in women compared to tenofovir disoproxil fumarate/emtricitabine (TDF/FTC). In the HPTN 084 open label extension, participants consented to CAB-LA injections during pregnancy. A nested sub-study evaluated the pharmacokinetics of total and unbound (bioavailable) CAB among a subset of participants who continued to receive CAB-LA injections to identify the need for dose adjustments during pregnancy.

METHODS

- Seventy-five HIV-negative participants who enrolled in the sub-study between 17 May 2022 and 13 September 2023 and received ≥ 4 CAB-LA injections both in the year prior to and during pregnancy were evaluated (**Table 1**).
- Total and unbound CAB concentrations were measured via liquid chromatographic-tandem mass spectrometric (LC-MS/MS) analysis using validated assays with lower limits of quantitation (LLOQ) of 25 ng/mL and 0.05 ng/mL, respectively.
- Total trough (C_{trough}) CAB concentrations were averaged within each participant over the pre-pregnant period and during each pregnancy trimester and then summarized.
- Unbound CAB C_{trough} concentrations were evaluated from the 6 months prior to pregnancy through the end of pregnancy.
- The percent unbound (% unbound) CAB was calculated by visit and then summarized.

Table 1. HPTN 084 Pregnancy PK Cohort Characteristics.

Median age (years)* (Q1, Q3)	28 (26, 32)
Median weight (kg)* (Q1, Q3)	59 (56, 78)
Median Body Mass Index (kg/m2)* (IQR)	27 (23, 32)
Pregnancy Outcome	
Full-term live birth	69/75 (92%)
Pre-term live birth	6/75 (8%)
Median number of CAB-LA injections in the year prior to pregnancy (range)	6 (4-7)
Number of CAB-LA injections during pregnancy	
4	48/75 (64%)
5	27/75 (36%)

*at pregnancy report date

Unbound (bioavailable) CAB concentrations remain above pharmacologic targets throughout pregnancy, supporting that CAB-LA dose adjustments are *not* needed during pregnancy

RESULTS

From the pre-pregnant period through the 3rd trimester, there was a median 26% reduction (IQR: 2%, 40%) in total CAB C_{trough} concentrations, from 2.3 µg/mL to 1.6 µg/mL. Median unbound CAB C_{trough} concentrations in the 6 months prior to pregnancy and the 1st, 2nd, and 3rd trimesters were 4.39 (IQR: 3.16, 5.08), 4.69 (IQR: 3.56, 5.89), 3.43 (IQR: 2.82, 5.02), and 3.74 (IQR: 2.63, 5.72) ng/mL, respectively (**Table 2**). Among this cohort, 98% of unbound CAB concentrations remained above the unbound pharmacologic threshold of 1.627 ng/mL, which is the 4x-IC_{90} for unbound CAB. For participants with total CAB concentrations less than the 4x PA-IC90 (664 ng/mL), unbound CAB concentrations remained above the 4x-IC_{90} in the third trimester (**Figure 1**). Within the entire PK cohort, median % unbound CAB C_{trough} increased from 0.16% (IQR: 0.12%, 0.22%) during the pre-pregnant period to 0.24% (IQR: 0.20%, 0.32%) in the 3rd trimester, suggesting an overall increase in the relative amount of bioavailable drug throughout pregnancy (**Figure 2**).

Table 2. Total and Unbound CAB C_{trough} concentrations prior to and throughout pregnancy.

	Pre-Pregnancy	1st Pregnancy Trimester	2nd Pregnancy Trimester	3rd Pregnancy Trimester
Number of participants (n)	75	74	75	75
Median Total CAB C_{trough} (µg/mL) (IQR)	2.3 (1.5, 2.8)	2.5 (2.1, 3.1)	1.8 (1.4, 2.3)	1.6 (1.3, 2.0)
Median Unbound CAB C_{trough} (ng/mL) (IQR)	4.39 (3.16, 5.08)	4.69 (3.56, 5.89)	3.43 (2.82, 5.02)	3.74 (2.63, 5.72)
Participants with Unbound CAB C_{trough} <4x IC_{90}	3/75 (4%)	3/71 (4%)	2/75 (3%)	4/72 (6%)
Median Percent Unbound (%Unbound) (IQR)	0.16% (0.12,% 0.22%)	0.22% (0.18%, 0.26%)	0.18% (0.14%, 0.24%)	0.24% (0.20%, 0.32%)

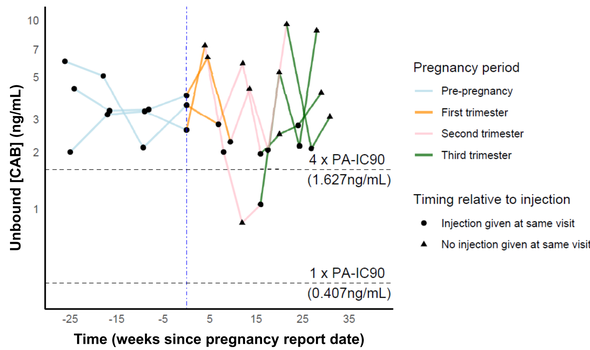

Figure 1. Unbound CAB concentration profiles for PK sub-study participants (n=3) whose total CAB concentrations fellow below the protocol-specified pharmacologic target (4x PA-IC_{90}; 0.664 mcg/mL) during pregnancy.

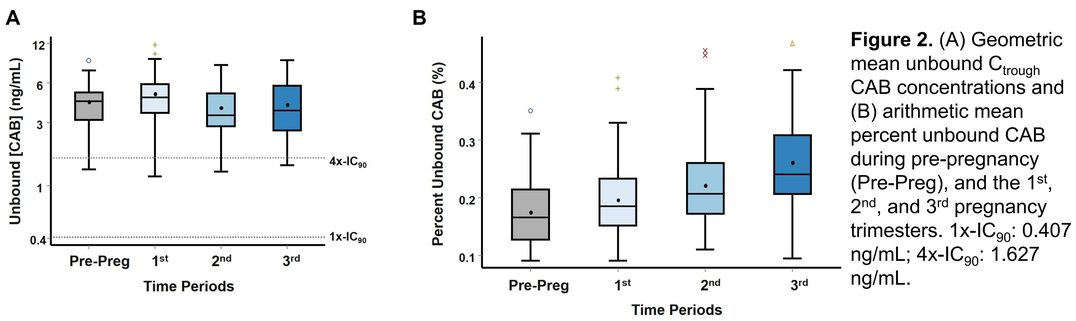

Figure 2. (A) Geometric mean unbound C_{trough} CAB concentrations and (B) arithmetic mean percent unbound CAB during pre-pregnancy (Pre-Preg), and the 1st, 2nd, and 3rd pregnancy trimesters. 1x-IC_{90}: 0.407 ng/mL; 4x-IC_{90}: 1.627 ng/mL.

CONCLUSIONS

While declines in total CAB concentrations throughout pregnancy were observed, changes in unbound CAB concentrations were non-clinically relevant, and the % unbound CAB increased from the pre-pregnant period through the 3rd trimester. These data provide pharmacologic support that CAB-LA dose adjustments are not needed during pregnancy.

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