Evaluation of CAB-LA Safety and PK in Pregnant Women in the Blinded Phase of HPTN 084

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BACKGROUND

HPTN 084 is a phase 3 randomized, double-blind, double-dummy trial that showed that long-acting injectable cabotegravir (CAB-LA 600 mg Q8 weekly) was superior to tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in preventing HIV in women in sub-Saharan Africa. Participants were required to use long-acting contraception; pregnancies however occurred during the trial. We report on the safety and pharmacokinetics of CAB-LA in women who became pregnant during the blinded phase of HPTN 084.

METHODS

If a participant had a positive pregnancy test, blinded study product was withheld and she was offered open-label TDF/FTC. Positive pregnancy tests were confirmed at a 2nd visit four weeks later, and, if CONFIRMED, TDF/FTC was continued through pregnancy outcome and until cessation of breastfeeding. Participants with CONFIRMED pregnancy were unblinded to study arm, and continued follow-up visits; Live infants were assessed at birth and 12 months. Adverse events (AEs) post-confirmation of pregnancy were compared between study arms from time of first positive pregnancy test to last pregnancy follow up visit. Only participants who received at least one injection were included in the safety analysis. The apparent terminal phase half-life (t1/2app) of CAB-LA in pregnant women in HPTN 084 (n=18/29; with at least ≥3 CAB samples available after injection cessation) was compared to non-pregnant women from HPTN 077 (n=39), a phase 2 safety and pharmacokinetics study. Multivariate linear regression assessed factors associated with t1/2app

TABLE 1. Pregnancy incidence, by study group

	CAB LA N=1614	TDF/FTC N=1610
No. of pregnancies*	39	37
Person-years	1915.5	1980.9
Incidence rate (95% CI)	2 (1.4, 2.8)	1.9 (1.3, 2.6)
No. CONFIRMED pregnancies	29	20
Person years	1915.5	1980.9
Incidence rate (95% CI)	1.5 (1.0, 2.2)	1.0 (0.6, 1.6)

** Participants had at least one positive pregnancy test*

Residual CAB-LA was generally well tolerated in pregnant women. The $t_{1/2app}$ was comparable between pregnant and non-pregnant women. Ongoing studies will examine the safety and pharmacology of CAB-LA in women who choose to continue CAB-LA through pregnancy.

RESULTS - SAFETY

There were 49 confirmed pregnancies (29 CAB, 20 TDF/FTC) in 48 participants during the blinded phase of the study. Pregnancy incidence was 1.3 per 100 person-years (py). CAB-LA participants (n=6) experienced more pregnancy-associated AE than TDF/FTC participants (n=1). All pregnancy-associated AE (n=10) were judged as unrelated to study product and grade 1-3. No congenital anomalies were observed. Of the 43 participants (26 CAB-LA, 17 TDF/FTC) with confirmed pregnancy who received at least one injection, the incidence of ≥ grade 2 AEs in the CAB arm was 113/100 py (95% CI: 69.3-185.4/100 py) vs. 166/100 py (95% CI: 102.2-271.0/100 py) in the TDF/FTC arm (p=0.064).

TABLE 2. Adverse events – pregnancy, puerperium and perinatal conditions

	CAB LA N = 9 events	TDF/FTC N = 1 event
Hyperemesis gravidarum	2	1
Pregnancy-induced hypertension	1	0
Pre-eclampsia	1	0
Oligohydramnios	1	0
Premature rupture of membranes	2	0
Incomplete abortion	2	0

Three participants in the CAB group reported two AE each; a total of 7 participants reported 10 AE

TABLE 3. Pregnancy outcomes, by study group

	CAB LA N=29	TDF/FTC N=20
Known pregnancy outcomes*	27	18
Live births	22 (82%)	14 (79%)
Pregnancy Loss - total	5 (18%)	4 (22%)
>=37 weeks	0	0
20-36 weeks	1	3
<20 weeks	4	1
Ectopic pregnancies	0	0
Congenital anomalies**	0	0

**No obtainable outcome for 4 pregnancies, 2 CAB 2TDF/FTC*
*** Congenital anomalies not assessable in 5 cases with early pregnancy loss CAB 3, TDF/FTC 2*

RESULTS - PHARMACOKINETICS

FIGURE 1. Linear regression of $\log_{10}$ [CAB] vs. time, for HPTN 084 and HPTN 077

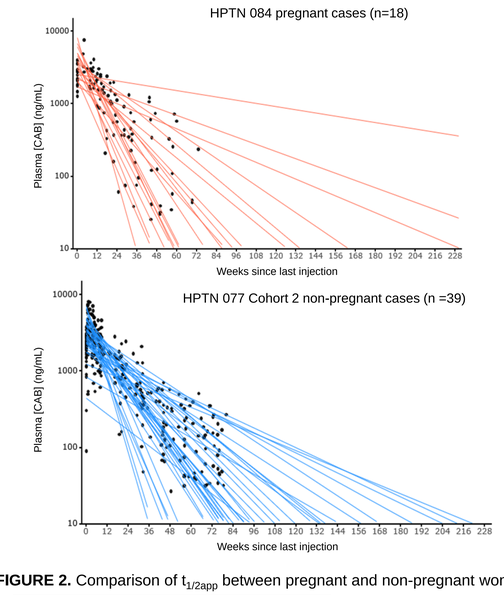
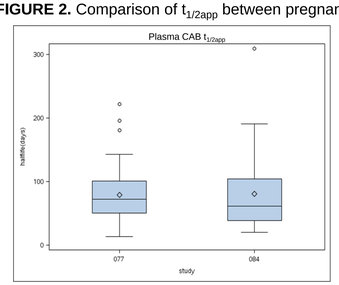


FIGURE 2. Comparison of $t_{1/2app}$ between pregnant and non-pregnant women



The CAB $t_{1/2app}$ geometric mean was 62.0 days (95% CI 43.7-88.0) in HPTN 084 pregnant women compared to 64.3 days (95% CI: 51.1-80.8) in HPTN 077 non-pregnant women.

- Age, weight, race, and pregnancy status were not significantly associated with $t_{1/2app}$.
- Body mass index (BMI) >27.2 kg/m^2 was associated with a longer CAB $t_{1/2app}$ (fold-change:1.49; p=0.069).

CONCLUSIONS

Residual CAB-LA was generally well-tolerated in pregnant women. The $t_{1/2app}$ was comparable between pregnant and non-pregnant women. Ongoing studies will interrogate CAB-LA concentrations in women who choose to receive injections throughout pregnancy.

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