Sex Differences in Cabotegravir Pharmacokinetics in the SEARCH Study in Kenya and Uganda

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BACKGROUND

- Long-acting injectable cabotegravir (CAB-LA) is highly effective for HIV prevention.
- Phase 2a trials found sex differences in CAB pharmacokinetics (PK). Male participants had higher CAB trough concentrations than females after the first injection but lower troughs at subsequent injections.
- In the HIV treatment setting, sex differences in CAB troughs were also observed in a large European cohort of patients receiving LA cabotegravir/rilpivirine.
- Understanding sex differences in plasma PK as CAB-LA is rolled out across multiple global settings for both PrEP and treatment is important for optimal dosing and potential forgiveness of late injections.
- We report the first analysis of sex differences in CAB PK using a direct-to-inject strategy in a high HIV-burden setting: Kenya and Uganda.

METHODS

- Pharmacokinetic analysis of samples collected at injection visits from participants receiving CAB-LA 600 mg IM in the SEARCH Dynamic Choice HIV Prevention study (NCT05549726; PMID 39395424).
- CAB trough concentrations in plasma were analyzed via reverse-phase liquid chromatography-tandem mass spectrometry (LC/MS/MS) using a validated analytical method. The plasma assay has a linear dynamic range of 0.0100-20.0 µg/ml, with a lower limit of quantitation of 0.0100 µg/ml.
- Among randomly-sampled participants with injections ≤28 days after target dates, plasma CAB trough concentrations were compared by sex, and analyzed in relation to published PK targets of protein-adjusted concentrations for 90% inhibition of virus ($PAIC_{90}$).

Table 1. Cabotegravir trough concentrations (median, IQR) by sex and injection week

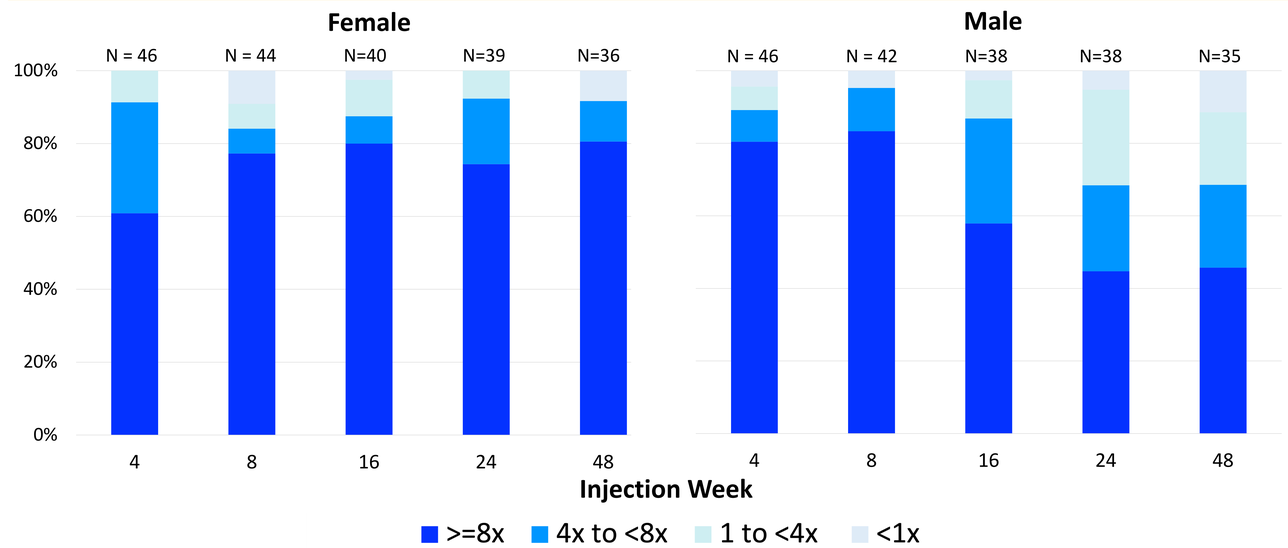
	Female		Male		
Week	**N**	**C_{trough} (µg/ml)**	**N**	**C_{trough} (µg/ml)**	**p-value**
4	46	1.5 (1.0 - 1.8)	46	2.1 (1.4 - 2.5)	**0.001**
8	44	2.6 (1.4 - 3.5)	42	2.3 (1.8 - 3.2)	0.75
16	40	2.0 (1.5 - 2.9)	38	1.7 (0.9 - 2.2)	0.06
24	39	1.8 (1.3 - 2.9)	38	1.1 (0.4 - 1.7)	**<0.001**
48	36	1.8 (1.5 - 2.4)	35	1.1 (0.6 - 2.1)	**0.02**

RESULTS

- 49 women: median age 33 years (IQR 28-39), BMI 24.1 kg/m^2 (20.7-26.8), weight 61 kg (56-68)
- 48 men: median age 33 years (IQR 24-41), BMI 23.6 kg/m^2 (21.0-26.0), weight 65 kg (57-72)
- On-time injections: 95% given within 7 days of target date, 2% within 8-14 days, 3% within 15-28 days
- **Table 1:** At week 4, median CAB trough concentrations were *higher* among men compared to women
- At subsequent injection weeks, median CAB troughs were *lower* among men than women, with significant differences at weeks 24 and 48
- **Figure 1:** At least 80% of men and women had CAB through levels ≥ 4x $PAIC_{90}$ prior to week 24
- At weeks 24 and 48, CAB levels were ≥ 4x $PAIC_{90}$ among 92% of women and 68% and 69% of men
- Levels were ≥ 8x $PAIC_{90}$ among 74% and 81% of women at weeks 24 and 48, and 45% and 46% of men

In the first PK study of CAB-LA PrEP in East Africa, median CAB trough concentrations were *higher* among men than women after the first injection, but *lower* among men than women after subsequent injections. Despite these findings, no participants, including men, acquired HIV in the trial intervention arm.

Figure 1. Cabotegravir trough concentrations in relation to $PAIC_{90}$ by sex



CONCLUSIONS

- In the first PK study of CAB-LA PrEP with a direct-to-inject strategy in East Africa, CAB trough concentrations were higher among men than women after the the first injection, but lower after subsequent injections.
- At weeks 24 and 48, only half to two-thirds of men had CAB trough levels above published PK targets.
- Although no participants on CAB-LA, including men, acquired HIV during the trial, adhering to the CAB-LA injection schedule may be particularly important for men to maintain adequate CAB levels.
- These results highlight the importance of examining sex differences and forgiveness in PK with current and forthcoming LA-PrEP, as well as determining thresholds for protection in routine care settings.

PLAIN LANGUAGE SUMMARY

In this study, we measured levels of cabotegravir in plasma among individuals receiving long-acting PrEP with cabotegravir. Even though cabotegravir levels were lower among men than women after receiving injections for several months, no participants on this form of PrEP acquired HIV during the study.

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