Hormonal Contraceptives Do Not Alter Cabotegravir PK in HIV Uninfected Women: HPTN 077

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BACKGROUND

- Long-acting injectable cabotegravir (CAB LA) is a strand-transfer integrase inhibitor, currently in development for HIV prevention and treatment
- Hormonal contraception is crucial for women of reproductive potential who are at-risk or infected with HIV to prevent the vertical transmission of HIV[1]
- Unexpected drug-drug interactions between ARVs and hormones for contraception or cross-sex therapy have been noted in several previous studies:
  - Oral contraceptives containing ethinyl estradiol/desogestrel reduced efavirenz serum concentrations by 18% (p=0.03)[2]
  - Ethinyl estradiol/norelgestromin transdermal patch with lopinavir/ritonavir resulted in lower ritonavir maximum concentration and AUC (8% and 24%, respectively, p=0.03)[3]
  - Medroxyprogesterone acetate has been noted to decrease intracellular levels of tenofovir-diphosphate concentrations in blood CD4+ T cells, resulting in reduced anti-HIV activity of tenofovir[4]
  - Estrogen with or without anti-androgen use has been noted to result in 13-38% reduction in tenofovir exposure (AUC)[5-6]
  - In a fixed sequence crossover study, oral CAB was shown to have no impact on oral ethinyl estradiol or levonorgestrel[7]
- Given the widespread use of hormones for both contraception and cross-sex hormone therapy, understanding potential DDIs between sex hormones and ART is critical to the complete understanding of safety, efficacy, and acceptability of novel treatment and prevention paradigms

METHODS

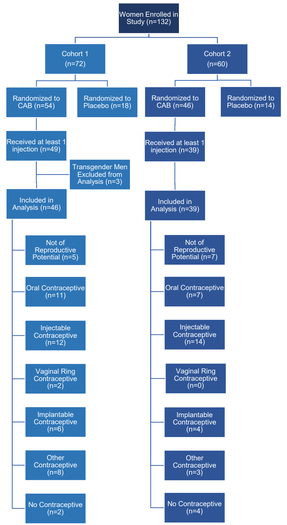
STUDY POPULATION AND DESIGN

- We performed a secondary analysis of 85 cisgender women who were enrolled and randomized to CAB in HPTN 077, a Phase 2a multicenter study that enrolled HIV-uninfected, low-risk individuals in Malawi, Brazil, South Africa, and the United States from February 2015 – May 2016[8]
- Participants received CAB 30mg orally daily x 4 weeks, followed by
  - CAB LA 800mg IM every 12 weeks for 3 injections (Cohort 1), or
  - CAB LA 600mg for 5 injections (Cohort 2)
    - First two injections separated by 4 weeks, the remainder by 8 weeks
  - Primary endpoint was at week 41 for both cohorts
- CAB plasma concentration measurements were obtained at weeks:
  - 6, 9, 13, 18, 23, 30, 35, and 41 (Cohort 1)
  - 6, 10, 13, 18, 21, 26, 29, 34, 37, 41 (Cohort 2)
- Participants were followed 52-76 weeks subsequent to their final injection

STATISTICAL ANALYSIS

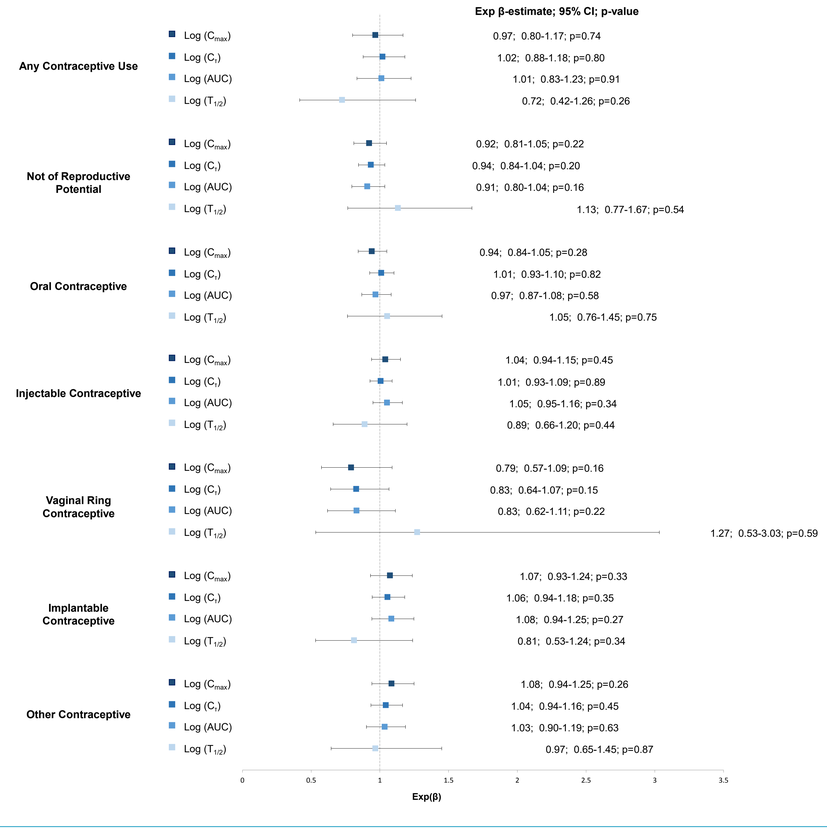
- Linear regression was used to evaluate pharmacokinetic (PK) parameters between hormonal contraception (use vs not based on self-report) and contraception type (oral, injectable, vaginal ring, implants, other)
  - As all women not of reproductive potential were on a hormonal contraceptive, they were included as a separate group in the analysis
- Peak concentration [C_{max}], trough [C_t], exposure after the last injection [$AUC_{0\text{-}t}$] were estimated for each injection, and apparent terminal half-life after the last injection [$T_{1/2app}$] was included in the analysis.
  - A linear mixed model was used to assess associations of hormonal contraception between C_{max}, C_t, and $AUC_{0\text{-}t}$ in order to account for correlations of these PK parameters across injections
  - Linear regression analysis was utilized for $T_{1/2app}$
- Cohorts 1 and 2 were combined in univariate and multivariate analysis
- Multivariate analysis assessed baseline covariates associated with PK parameters, adjusting for BMI and CAB dose cohort
- P-values ≤ 0.05 were considered statistically significant

Study Consort Diagram of Women Included in Analysis and Contraceptive Use



RESULTS

Multivariate Regression Analysis of Contraceptive Use (yes vs no), Contraceptive Type and PK Parameters [log(C_{max}), log(C_t), log(AUC), and log($T_{1/2}$)], Controlling for BMI and Cohort



Univariate Regression Analysis of Contraceptive Use, Contraceptive Type and Select PK Parameters [log (C_t) and log ($T_{1/2}$)]

	N	PK Parameter	Exp(β)	95% CI	p Value
Contraceptive Use	79	log (C_t)	0.99	0.84-1.17	0.94
		log ($T_{1/2}$)	0.83	0.50-1.38	0.47
Not of Reproductive Potential	12	log (C_t)	0.95	0.84-1.06	0.33
		log ($T_{1/2}$)	1.15	0.78-1.70	0.48
Oral Contraceptive	18	log (C_t)	1.00	0.90-1.10	0.92
		log ($T_{1/2}$)	1.08	0.78-1.49	0.64
Injectable Contraceptive	26	log (C_t)	1.00	0.92-1.09	0.98
		log ($T_{1/2}$)	0.95	0.71-1.27	0.74
Vaginal Ring Contraceptive	2	log (C_t)	0.81	0.62-1.05	0.12
		log ($T_{1/2}$)	1.19	0.50-2.83	0.69
Implantable Contraceptive	10	log (C_t)	1.07	0.94-1.21	0.30
		log ($T_{1/2}$)	0.79	0.52-1.21	0.28
Other Contraceptive	11	log (C_t)	1.04	0.93-1.17	0.46
		log ($T_{1/2}$)	0.89	0.60-1.32	0.57

CONCLUSIONS

- Among HIV-uninfected females in HPTN 077, use of hormonal contraception (regardless of type used) did not alter the CAB LA concentration profile during injections or during the pharmacokinetic tail in either univariate or multivariate analysis
- In the multivariate analysis, the sample size of this study can rule out an effect size of a 2-fold change for log(C_{max}), 2-fold change for log(C_t), 1.8-fold change for log(AUC), and 2.1-fold change for log($T_{1/2}$) with 80% power using a 5% type 1 error rate for any hormonal contraceptive use vs not.
- No significant associations were found between hormonal contraception use and PK parameters among the women who received CAB injections in HPTN 077
- The findings in this study are consistent with the expectation that there would not be an interaction of hormonal contraception on CAB PK, since CAB is metabolized by UGT1A1 and A9[9].
- While we did not measure the effect of CAB on hormone concentration profiles in this study, it is expected that there would be no interaction, as oral CAB had no significant effect on PK profiles of levonorgestrel/ethinyl estradiol oral contraceptives in a prior fixed-sequence crossover study [7]
- Future research regarding the effect of CAB on sex hormone levels gender-affirming therapy is warranted

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