

## Cabotegravir is Not Associated with Weight Gain in HIV-uninfected Individuals in HPTN 077

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## ABSTRACT

Studies in HIV-infected individuals suggest excess weight gain with integrase inhibitor-based antiretroviral therapy. HPTN 077 evaluated changes in weight and fasting metabolic parameters in HIV-uninfected individuals randomized to cabotegravir or a placebo. No differences between arms were found for change in weight or fasting metabolic parameters overall or for subgroups.

Keywords: Cabotegravir, CAB, Weight gain, HIV uninfected

## Background

Antiretroviral treatment (ART) that contains an integrase inhibitor has been associated with weight gain and increased waist circumference, with changes of greater magnitude seen among women, black patients, and those with lower CD4 and higher HIV RNA prior to starting ART [1-7]. Some studies have observed a mitigating effect of tenofovir disoproxil fumarate (TDF) in those regimens [1], and these changes have been associated with increases in body mass index (BMI) category [8] – a change that has been associated in other studies with morbidity and mortality [9].

Cabotegravir (CAB) is a novel integrase inhibitor in development for HIV prevention, and as part of combination ART for treatment. CAB is available both as an oral tablet for daily administration (being developed only for lead-in to the injectable product) and as a long-acting suspension for monthly or every-other-month intramuscular injection [10]. Weight changes for HIV-infected participants in trials of CAB as part of combination ART have not yet been published.

HIV Prevention Trials Network study 077 (HPTN 077) was a Phase 2a safety, tolerability, and pharmacokinetic study that enrolled 199 HIV-uninfected low risk participants at 8 sites globally [11]. The study provides a unique opportunity to evaluate changes in weight and metabolic parameters among participants exposed to long-acting injectable CAB (CAB LA) or a placebo (PBO), absent HIV infection or additional antiretroviral agents. We performed a post-hoc analysis to explore the hypothesis that changes in weight and metabolic parameters would not be different between participants in the CAB and PBO study arms.

## METHODS

### Study design

In HPTN 077, participants were randomized 3:1 to CAB or a PBO course, during which they received a daily oral tablet for 4 weeks, a one-week hiatus, and then a series of injections with a primary safety and tolerability endpoint 41 weeks after study entry. Two dose cohorts were enrolled sequentially, the first with an injection phase consisting of three quarterly injections of 800mg of CAB (or a 0.9% saline placebo), and the second characterized by five total injections of 600 mg of CAB at 8-week intervals after a 4-week initial separation. Participants were then followed for 48-72 weeks after their final injection.

### Assessments

Weight was measured at study entry, during oral product administration at weeks 2 and 4, and during injectable product administration at weeks 5, 17, 19, 29 or 33, and 41 (Figure).

Demographics were collected at baseline, and BMI was calculated from baseline height measurement and Week 0 (W0) and Week 41 (W41) weight measurements. Fasting glucose and fasting lipids were collected at W0 and W41.

### Analysis

Wilcoxon rank sum tests were used to compare distributions of intraparticipant changes in weight and metabolic parameters; only participants with paired W0 and W41 data available for a given parameter were included. Generalized estimating equations were used to model longitudinal weight data over time. Mean modeled intraparticipant weight changes were compared between CAB and PBO groups as an additional sensitivity analysis to the primary comparison. The GEE model included all 177 participants and available weight data at all available timepoints of interest (above) for a given participant.





parameters were also not different between CAB and PBO treated participants (Supplementary Figure 1 Panel C). No participant met the fasting glucose criterion for diabetes.

### Outcomes

Among the 146 participants with paired weights, between W0 and W41 the median increase in weight for CAB treated participants was 1.1 (IQR -0.9, +3.0) kg; median 1.0 (IQR -1.2, +3.2) kg was gained by PBO treated participants ( $\Delta=+0.1$  kg,  $p=0.66$ ). The distribution of weight changes across the 41 week treatment period did not differ between CAB and PBO-treated participants, nor when divided into the W0-W4 oral phase ( $\Delta=+0.3$  kg,  $p=0.6$ ) and the W5-W41 injection phase ( $\Delta=+0.2$  kg,  $p=0.65$ ). A 5% or greater increase in weight from W0 to W41 was seen in 24 (22%) CAB participants and 7 (18%) of PBO participants ( $p=0.62$ ).

Distributions of changes in weight from W0 to W41 were also not different among racial and ethnic subgroups, nor by sex at birth, injectable product dose cohort, BMI category (greater than or less than or equal to the overall study population median), or baseline current smoking status (Supplementary Figure 2). Distributions of changes in weight were also not different across geographic region (US, Brazil, sub-saharan Africa).

Frequency of transitions between BMI categories (using standard definitions) were not significantly different between arms (Supplementary Figure 1 Panel B). GEE models of all available weight data over time were consistent with the sparse analysis using only W0 and W41 data (Supplementary Tables 1 – 3).

Distributions of changes in fasting glucose and lipid parameters also were not different between CAB and PBO treated participants (Supplementary Figure 3).

## Discussion

Clinical experience, observational cohort data and randomized trials strongly suggest but do not confirm an association of integrase inhibitor-based antiretroviral therapy with weight gain.

Observational data from treatment studies in persons living with HIV have described transitions in BMI category among integrase inhibitor-(INI) treated participants [8] that have the potential to increase risk for metabolic complications and increased risk of cardio- and cerebrovascular disease and altered glucose homeostasis. These data are potentially confounded by the presence of HIV infection and its inflammatory sequelae, a return to health phenomenon, as well as potential mitigating or exacerbating effects of nucleoside reverse transcriptase inhibitors, used as “backbones” of ART regimens.

We explored changes in weight and fasting metabolic parameters assessed as part of the Phase 2 development program of CAB LA for HIV prevention. Absent HIV infection and potentially confounding additional antiretroviral drugs, we found no significant differences in changes in weight or fasting metabolic parameters between participants randomized to CAB or PBO. The observed weight changes were modest (approximately 1.0 kg in each arm over approximately 9.5 months).

These results suggest that the observed excess weight increases for INI-treated HIV-infected individuals may be attributable to an interaction between integrase inhibitors and HIV itself or its inflammatory milieu – and/or an interaction between integrase inhibitors and other anti-HIV agents.

Important limitations to this analysis are its post-hoc exploratory design, non-standardization of weight measurement across study sites, and the modest sample size of the overall study and the subgroups analyzed. Two ongoing double-blind, double-dummy Phase 3 HIV prevention trials, HPTN 083 (NCT02720094) and HPTN 084 (NCT03164564), with a planned total enrollment of 7,700 participants will provide more definitive data to address this question.

The modest sample size limited our ability to rule out weight change differences smaller than approximately 2.4 kg between arms – however, if these negative results are confirmed in the larger ongoing Phase 3 prevention studies of CAB, it is possible that the weight increases seen in treatment studies of HIV-infected individuals are attributable to differential effects of integrase inhibitors on the HIV-affected immunologic milieu, a molecule-specific (rather than class) effect, and/or bystander activity of other ARVs. It is also possible that participants who did not receive the full complement of injections in each cohort (Figure Panel A), and therefore were exposed to waning CAB levels over the observation period further diluted any metabolic effects. TDF/FTC was associated with a 5% or greater unintentional weight loss in the iPrEX study [12]; absence of weight gain, if confirmed, could increase the acceptability of INI-based PrEP. While we did not observe a difference in fasting glucose between arms, we did not collect fasting insulin / HOMA-IR, a more sensitive measure for detecting changes in glucose tolerance.

In a moderately sized randomized study of CAB vs. PBO in HIV-uninfected participants, no differences in changes in weight or fasting metabolic parameters were apparent between study arms. Ongoing Phase 3 efficacy studies of CAB for HIV prevention will provide an opportunity to further examine these potential relationships.

Notes:

#### Acknowledgements

The study team thanks the study participants and their families; the clinical research staff at the 8 sites conducting the study; and Carlee Moser, PhD for her helpful discussions and review of the manuscript.

#### Financial Support

This work was supported by National Institute of Allergy and Infectious Diseases of the National Institutes of Health [grant numbers UM1AI068619, UM1AI068613, and UM1AI068617]. ViiV Healthcare provided study products for the conduct of HPTN 077.

#### Conflicts of Interest

RJL received personal fees from Gilead Sciences, Merck Inc, and Roche; JJE received grants from National Institutes of Health and grants and personal fees from ViiV Healthcare, Gilead Sciences, Merck, and Janssen; HD received personal fees from Adcock Ingram South Africa and MSD-South Africa, and support from MSD-South Africa and Pfizer; MM received grants from NIH/DAIDS/HPTN; AYL received support from Gilead Sciences; DAM received support from ViiV Healthcare; AR received support from ViiV Healthcare; MSC received support from Merck and Gilead; JSC received grants from Theratechnologies.

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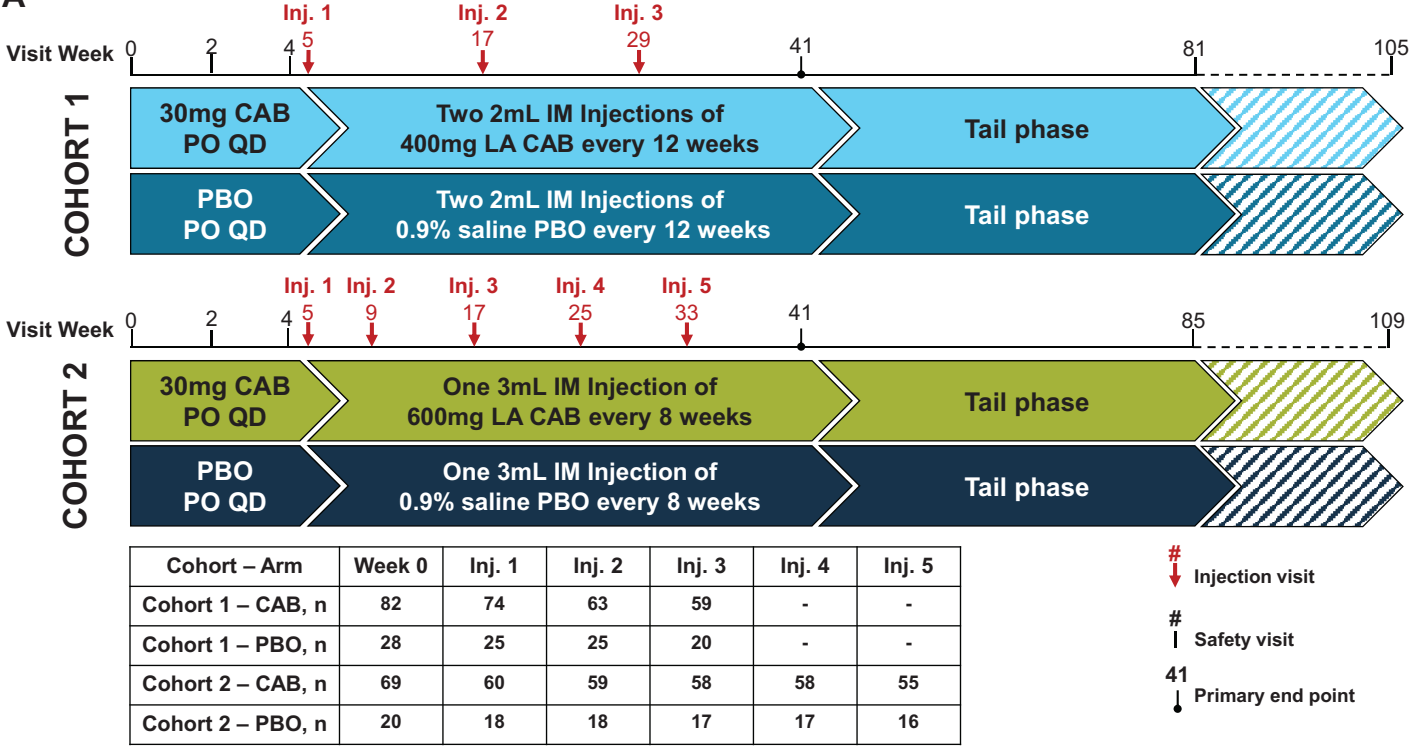
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Figure. A, HPTN 077 study design. B, Median participant weight by study arm over time.

Abbreviations: Inj, Injection; CAB, Cabotegravir; PO, by mouth (orally); QD, everyday; IM, intramuscular; PBO, Placebo

**A**



**B**

