

## ICAP Journal Club

ICAP's Journal Club is designed to inform ICAP staff and colleagues of the latest scientific literature by providing a succinct summary and critical analysis of important studies, and by discussing the implications of the research on clinical work.

### Article

Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. *N Engl J Med*. 2021;385(7):595-608.

<https://www.nejm.org/doi/full/10.1056/NEJMoa2101016>

### Study Summary

The HIV Prevention Trials Network (HPTN) 083 trial was a phase 2b-3, multicenter, double-blind, randomized controlled trial that compared the safety and efficacy of long-acting injectable cabotegravir (CAB-LA) to daily oral tenofovir disoproxil fumarate-emtricitabine (TDF-FTC) as HIV pre-exposure prophylaxis (PrEP) in cisgender men who have sex with men (MSM) and transgender women (TGW) who have sex with men.

### Study Setting

- Forty-three clinical trial sites in the United States, Latin America, Asia and Africa.

### Methods

- MSM and TGW women who have sex with men were eligible to participate if they were  $\geq 18$  years of age; considered at high risk for HIV infection; had a negative HIV serologic test at enrollment and an undetectable HIV RNA viral load  $\leq 14$  days before trial entry; had a creatinine clearance of  $\geq 60$  ml/min and were in general good health.
- Participants were excluded if they used illicit intravenous drugs  $\leq 90$  days before enrollment, previously were in the active treatment group of an HIV vaccine trial, or had a coagulopathy, buttock implants or fillers, a seizure disorder, a corrected QT interval of  $> 500$  msec, a positive hepatitis B surface antigen test or hepatitis C antibodies.
- Participants were randomly assigned (1:1) to receive either active cabotegravir (an integrase strand-transfer inhibitor [INSTI]) with TDF-FTC placebo (cabotegravir group) or active TDF-FTC with cabotegravir placebo (TDF-FTC group).
- The trial consisted of three phases:
  1. Oral-tablet lead-in phase: participants received two masked oral tablets (one active and one placebo) daily for five weeks. Active cabotegravir was given as a 30 mg tablet, and active TDF-FTC was given as a fixed-dose combination of 300 mg of TDF plus 200 mg of FTC. Participants who had  $\geq 50\%$  adherence to the

tablets, as determined by pill count, and had acceptable safety laboratory results progressed to the next phase.

2. Injection phase: participants received a supply of daily oral tablets and an intramuscular injection at the start of the phase, four weeks after the first injection and then every eight weeks up to week 153. CAB-LA was administered as a single 3-ml injection containing 600 mg of cabotegravir. Placebo for CAB-LA was an injectable fat emulsion that was visually similar.
  3. Tail phase: participants received open-label TDF-FTC for 48 weeks, beginning eight weeks after the final injection, to continue HIV PrEP coverage during the tail phase when plasma cabotegravir drug concentrations were in terminal decline.
- Additional evaluation visits were at weeks 2 and 4 during the oral-tablet lead-in phase, at weeks 6 and 10, then two weeks after each injection in the injection phase, and quarterly in the tail phase.
  - Visits included regular HIV antigen and antibody tests; assessment of adverse events, including injection site reactions and safety laboratory tests; collection and storage of plasma samples; adherence and risk-reduction counseling; and interviewer-led and computer-assisted structured interviews to evaluate adherence, sexual behaviors, alcohol and drug use, and acceptability of the oral tablets and injections.
  - Among participants with confirmed HIV infection, additional testing was performed retrospectively to determine the timing of infection and to assess HIV resistance mutations, and plasma cabotegravir concentrations were measured in all samples obtained from those in the cabotegravir group.
  - The primary efficacy endpoint of the trial was incident HIV infection.
  - The primary safety endpoint was the occurrence of an adverse event of grade 2 or higher, evaluated among those who had received at least one dose of any of the oral tablets or injections.
  - A cohort of 390 randomly selected participants in the TDF-FTC group had tenofovir concentrations measured in plasma and intraerythrocyte tenofovir–diphosphate concentrations measured in dried blood spots.
  - The noninferiority margin was set as a hazard ratio (HR) of 1.23 and the primary endpoint was evaluated using a modified intention-to-treat analysis, which excluded participants who were found to have HIV infection at enrollment.
  - Data presented are from interim analyses during the blinded phase of the trial, up to May 2020. The trial is currently ongoing with an open-label design.

#### Study Population and Follow-up

- Between December 2016 and March 2020, 6,333 people were screened for eligibility. Of these, 4,566 underwent randomization and were included in the intention-to-treat population, with 2,284 in the TDF-FTC group and 2,282 in the cabotegravir group.

- Participants had a median age of 26 years (interquartile range [IQR] 22-32), 87.4% identified as MSM, with demographic and clinical characteristics similar between the groups.
- Participant retention was 86.5% at one year, with a median follow-up of 1.4 years (IQR 0.8-1.9).
- Masked oral tablets and injections were permanently discontinued in 908 participants (19.9%), including 445 participants in the cabotegravir group and 463 in the TDF-FTC group.
- Median adherence during the oral-tablet lead-in phase was 96.6% (IQR 89.7-100.0) across both groups.
- Among the 390 participants evaluated in the TDF-FTC subgroup, 74.2% had plasma tenofovir concentrations consistent with receipt of daily TDF-FTC doses in the previous week and 72.3% had tenofovir–diphosphate concentrations in dried blood spots that were consistent with at least four TDF-FTC doses/week over the previous 1-2 months.

#### Primary Efficacy Outcome

- HIV infection was identified in 57 participants, including five who had undetected HIV infection at enrollment.
- In total, 52 participants were deemed to have acquired HIV after enrollment and were included in the primary efficacy analysis: 13 in the cabotegravir group (incidence, 0.41 per 100 person-years) and 39 in the TDF-FTC group (incidence, 1.22 per 100 person-years).
- The HR for incident HIV infection in the cabotegravir group compared to the TDF-FTC group was 0.34 (95% confidence interval [CI], 0.18-0.62;  $p < 0.001$ ), which met the criteria for superiority.
- The direction and overall magnitude of the effect were consistent across pre-specified subgroups and in a per-protocol analysis.
- Among incident HIV infections in the cabotegravir group, four were found to have occurred in participants with appropriately timed CAB-LA doses and expected plasma cabotegravir concentrations. Other infections either occurred before enrollment, with no recent exposure to cabotegravir or in the oral lead-in phase before cabotegravir injections. INSTI resistance mutations were detected in one of the four cases identified as a baseline infection and in four of nine incident cases that had a resistance test result.
- In the TDF-FTC group, two of the 39 incident HIV infections occurred when measured drug concentrations were consistent with good PrEP adherence. Four incident infections and two baseline infections had nucleoside or nucleotide reverse-transcriptase inhibitor mutations.

## Safety Outcomes

- Adverse events of grade 2 or higher were reported in 92.5% of the participants overall, with no marked differences between the groups. Most common was decreased creatinine clearance (71.4%) and increased creatine kinase (20.9%).
- Adverse events of grade 3 or higher were reported in 32.7% of participants and serious adverse events in 5.3% of participants overall, with similar frequency in the two groups.
- Permanent discontinuation of the oral tablets and/or injections owing to adverse events, other than injection-site reactions, occurred in 3.8% of participants overall, with a similar frequency in the two groups.
- Eleven participants died, with seven in the TDF-FTC group and four in the cabotegravir group (HR 0.57, 95% CI, 0.17-1.96). One death from cardiovascular disease in the TDF-FTC was considered to be related to the study medications.
- Injection-site reactions were reported in 81.4% of participants in the cabotegravir group and in 31.3% of participants in the TDF-FTC group.
- Injection-site reactions were mostly mild or moderate in severity and decreased in frequency over time.
- Of 10,666 injection-site reactions in the cabotegravir group, 60.8% were pain and 23.7% were tenderness; the events began a median of 1 day (IQR, 0-2) after injection and lasted a median of 3 days (IQR, 2-6).
- A mean annualized increase in body weight of 1.23 kg per year (95% CI, 1.05-1.42) was noted in the cabotegravir group, as compared with an increase of 0.37 kg (95% CI, 0.18-0.55) in the TDF-FTC group.

## Critical Analysis

The phase 2b–3, multicenter, double-blind, randomized controlled HPTN 083 trial found injectable intramuscular CAB-LA, administered every 8 weeks, to be superior to daily oral TDF-FTC in preventing incident HIV infections in MSM and TGW who have sex with men. Injection site reactions were common among those receiving CAB-LA, but there were no major safety concerns identified in either group.

The following points should be considered when interpreting the study findings:

- The trial's Data and Safety Monitoring Board reviewed the first pre-planned interim endpoint analysis in May 2020, and concluded that the results met the pre-specified criteria for stopping the trial early on the basis of efficacy. Subsequently the trial was switched to an open-label design, which is currently ongoing.

- Inadequate TDF-FTC adherence among some participants appeared to drive the overall finding of HIV incidence in that group, as TDF-FTC is known to be highly effective when taken daily.
- Although the majority of the participants in the cabotegravir group reported injection-site reactions, only 2.4% chose not to receive further injections as a result.
- Increased weight gain has been associated with the use of INSTIs. However, in this trial differences in weight change between the two groups were driven by weight loss in the TDF-FTC group in year 1, after which the weight changes were similar.
- This trial was limited to MSM and TGW who have sex with men. However, a similarly designed trial evaluating the efficacy of CAB-LA in cisgender women in Africa was recently unblinded early after showing superiority of CAB-LA over daily oral TDF-FTC (ClinicalTrials.gov number, NCT03164564). Additionally, the safety and acceptability of CAB-LA in adolescents is under evaluation (NCT04692077 and NCT04824131).
- No resistance was detected in the four cases with viral escape or HIV acquisition during the period of cabotegravir decay after the last injection (tail phase). Participants were closely monitored during this period; therefore, strategies to reduce the time from infection to diagnosis during the tail phase will be important in real-world implementation.

## Implications

The phase 2b–3, multicenter, double-blind, randomized controlled HPTN 083 trial found injectable intramuscular CAB-LA to be superior to daily oral PrEP in preventing incident HIV infections in MSM and TGW who have sex with men. This long-acting form of PrEP helps to overcome adherence challenges that are common with daily PrEP use, and is currently being studied in other important populations. Offering injectable CAB-LA as PrEP would require existing HIV prevention programs to develop new implementation approaches. Nonetheless, these results suggest the use of CAB-LA is an effective HIV prevention strategy, which has the potential to significantly reduce incident HIV infections and expand person-centered PrEP options.

*This article synopsis was written by Dr. Cassia Wells. Share your thoughts on this article or suggest an article for Journal Club by emailing her at [caw2208@columbia.edu](mailto:caw2208@columbia.edu).*