ICAP Journal Club

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Article

Delany-Moretlwe S, Hughes JP, Bock P, et al. **Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial**. *Lancet*. 2022;399(10337):1779-1789. https://doi.org/10.1016/S0140-6736(22)00538-4

Study Summary

The HIV Prevention Trials Network (HPTN) 084 trial was a phase 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 women.

Study Setting

- Twenty clinical research sites in Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, and Zimbabwe.

Methods

- Individuals were eligible to participate if they were assigned female sex at birth; were aged 18–45 years; reported ≥2 episodes of vaginal intercourse in the previous 30 days; were at risk of HIV infection based on a risk score; and agreed to use a long-acting reversible contraceptive method. In addition, all participants were required to have non-reactive HIV test results with a rapid antibody test and a laboratory-based antigen–antibody test, as well as undetectable HIV RNA ≤14 days before enrollment.
- Participants were excluded if they were pregnant or breastfeeding; had substantial renal, hepatic, or cardiovascular disease; had a history of seizures, coagulopathy, or allergy to any of the study products; or if they were previously enrolled in an HIV vaccine or monoclonal antibody trial.
- Participants were randomly assigned (1:1) to receive either active cabotegravir 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 5 weeks. Active cabotegravir was given as a 30 mg tablet, and active TDF–FTC was given as a fixed-dose combination of 300 mg TDF plus 200 mg FTC. Participants who had at least 50% adherence by pill count and acceptable safety laboratory results were permitted to progress to the next phase.

2. Injection phase: participants received an intramuscular injection at the start of the phase, a second injection 4 weeks later, and injections every 8 weeks thereafter up to week 185. CAB-LA was administered as a single 3 ml intramuscular gluteal injection containing 600 mg cabotegravir. Placebo for CAB-LA was an injectable fat emulsion that was visually similar. Participants were also supplied with oral pills (TDF-FTC or placebo).
3. Tail phase: participants received open-label daily TDF–FTC for 48 weeks, beginning 8 weeks after the final injection, to continue HIV PrEP coverage during the tail phase when plasma cabotegravir drug concentrations were in terminal decline.

- Assessments were done at weeks 2 and 4 during the oral tablet lead-in phase; 1 week after the initial injection, 4 weeks after the second and third injections, and at each injection visit thereafter during the injection phase; and quarterly in the tail phase.
- Visits included HIV testing with rapid antibody tests and laboratory-based HIV antigen-antibody immunoassay; assessment of adverse events, including physical examination and safety laboratory tests; collection and storage of plasma samples; adherence counseling; and behavioral risk assessments with computer-assisted self-interview. Participants were also tested for pregnancy before product dispensation.
- Specific injection site reaction assessments were done at weeks 6, 13, 21, and 42, although participants could report an injection site reaction at any visit.
- Participants received a comprehensive HIV prevention package, which included HIV risk-reduction counseling; offer of condoms, lubricants, and contraception; and treatment for symptomatic sexually transmitted infections (STIs), as well as laboratory-based STI testing every 6 months.
- If a participant became pregnant, injectable study product was withheld and daily open-label TDF-FTC was offered through the duration of pregnancy and breastfeeding. All pregnant participants were referred for a first-trimester ultrasound to assess for fetal anomalies and live infants were assessed 12 months after delivery for congenital anomalies.
- Plasma tenofovir and intraerythrocyte tenofovir–diphosphate concentrations were measured in a cohort of 405 randomly selected participants to evaluate oral TDF-FTC adherence.
- Among participants with confirmed HIV infection at the study site, samples were collected to assess CD4 cell count, viral load, and HIV drug resistance. Additional testing was performed retrospectively to determine the timing of HIV infection, presence of resistance mutations, plasma cabotegravir concentrations (cabotegravir group) and plasma tenofovir and intraerythrocytic tenofovir diphosphate concentrations (TDF-FTC group).
- The primary efficacy endpoint was incident HIV infection in phase 1 and 2 combined, and the primary safety endpoint was the occurrence of an adverse event of grade 2 or higher.
- Secondary and tertiary outcomes included HIV incidence in pre-specified subgroups (age, contraceptive use method and body mass index [BMI]), pregnancy incidence and outcomes, weight, and HIV drug resistance.
- The primary efficacy analysis was done using an intention-to-treat (ITT) population that included all participants who were randomized and confirmed as HIV-uninfected at

enrollment, according to a site-based HIV testing algorithm. The primary safety analysis included all participants who had received at least one dose of study product.

- Data presented are from interim analyses during the blinded phase of the trial, up to November 2020. The trial is currently ongoing with an open-label design.

Study Population and Follow-up

- Between November 2017 and November 2020, 4,878 participants were screened, of whom 3,178 were randomized and included in the ITT population (1,592 in the cabotegravir group and 1,586 in the TDF-FTC group).
- Participants had a median age of 25 years (interquartile range [IQR] 22–30), 99.8% self-identified as female, 54.7% reported ≥2 sex partners in the month before enrollment, 40.9% reported transactional sex, and 34.3% had a primary partner living with HIV or with an unknown HIV status.
- Median follow-up time was 1.24 years (IQR 0.92–1.56); 90.3% of planned visits were completed at month 12 and 86.0% were completed at month 24.
- Participants received a median of eight injections (5–11) and 6.0% discontinued the study product prematurely; discontinuation did not vary by study group.
- Of the 405 participants in the TDF-FTC group whose samples were evaluated for adherence, 55.9% (1084/1939) of the samples had quantifiable plasma tenofovir concentrations and 41.9% had tenofovir concentrations consistent with daily use. Intraerythrocytic tenofovir diphosphate concentrations were unquantifiable in 38.1% (456/1197) of dried blood spot samples and 18.0% of samples had tenofovir diphosphate drug concentrations consistent with at least four doses per week over the past month.
- An estimated 93.1% of person-years in the study were covered by injections, defined as injections received on time or with a delay of <2 weeks, with no difference by study group.

Efficacy Outcomes

- In the primary efficacy analysis, participants contributed 3,898 person-years and 40 HIV infections were identified.
- Four HIV infections were observed in the cabotegravir group (HIV incidence 0.20 per 100 person-years; 95% confidence interval [CI] 0.06–0.52) and 36 in the TDF-FTC group (1.85 per 100 person-years; 95% CI 1.3–2.57). The absolute risk difference between the cabotegravir and TDF-FTC groups was –1.6% (95% CI –1.0% to –2.3%).
- Participants in the cabotegravir group had an 88% lower risk of HIV infection compared with those in the TDF-FTC group (hazard ratio [HR] 0.12; 95% CI 0.05–0.31; p<0.0001), after adjusting for site and the group-sequential design.
- Two participants in the cabotegravir group with incident HIV infection reported no recent cabotegravir exposure and did not receive any cabotegravir injections. In the third participant, HIV infection was detected during the injection phase, however, retrospective testing indicated that this participant had HIV infection at study enrollment and was subsequently re-classified as a baseline infection. The fourth infection occurred during the

injection phase of the study in a participant with delayed injection visits, and her last injection was 16.1 weeks before the visit when HIV infection was detected.

- All 36 infections in the TDF-FTC group were incident infections and none of these cases had tenofovir and tenofovir diphosphate concentrations consistent with 6–7 doses per week; only one participant had drug concentrations consistent with partial adherence (4–6 doses per week).
- After exclusion of the baseline infection, incidence in the cabotegravir group was recalculated, in a post-hoc analysis, as 0.15 per 100 person-years (95% CI 0.03–0.45), with a revised HR of 0.09 (95% CI 0·04–0·27; p<0.0001).
- Results were consistent across subgroups of age, contraceptive use, and BMI at baseline.
- No major integrase strand transfer inhibitor (INSTI) resistance mutations were detected in any of the four HIV infections observed in the cabotegravir group.

Safety Outcomes

- Overall, 92.2% of participants reported a grade 2 or worse adverse event and there were no significant differences in the frequency of any grade 2 or higher adverse events by study group, apart from injection site reactions.
- Adverse events led to permanent discontinuation of blinded study medication in 1.2% of participants; 1.1% in the cabotegravir group and 1.4% in the TDF-FTC group.
- Sixty-six participants experienced at least one serious adverse event; 33 in the cabotegravir group and 33 in the TDF-FTC group. Only six serious adverse events were considered to be related to study product (two in the cabotegravir group and four in the TDF-FTC group). There were three deaths in the study, all in the cabotegravir group, but none were attributed to study product.
- Injection site reactions were reported in 38.0% of participants in the cabotegravir group, compared with 10.8% in the TDF-FTC group. Pain was the most commonly reported symptom, with 4.4% of injections in the cabotegravir group associated with pain, compared with 1.1% of injections in the TDF-FTC group.
- There were no discontinuations of study product due to injection site reactions and most injection site reactions diminished over time. In the cabotegravir group, injection site reactions were reported in 28.8% of participants at the first injection, decreasing to 1.9% of participants by the fourth injection.
- Overall, there were 49 confirmed pregnancies, with 29 in the cabotegravir group and 20 in the TDF-FTC group.
- Outcome data were available for 31 pregnancies at the time of the data lock, with the remainder of pregnancies ongoing. Most pregnancies resulted in a livebirth (13 of 18 in the cabotegravir group and 10 of 13 in the TDF-FTC group), with the remainder ending in pregnancy loss (spontaneous or induced). No congenital anomalies were observed.
- In the cabotegravir group, there was a small but significant increase in average initial weight gain relative to the TDF-FTC group (0.4 kg; 95% CI 0·27–0·51; p<0.0001). Subsequently both groups showed weight gain, with a mean increase of 2.4 kg per year (95% CI 1.9–3.0) in the cabotegravir group compared with 2.1 kg per year (95% CI 1.9–2.4) in the TDF-FTC group (p=0.041).

Critical Analysis

The phase 3, multicenter, double-blind, randomized controlled HPTN 084 trial found injectable intramuscular CAB-LA, administered every 8 weeks, to be superior to daily oral TDF–FTC in preventing incident HIV infection in women. Injection site reactions were common in the group 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:

- During the second pre-planned interim analysis in November 2020, the trial's Data and Safety Monitoring Board concluded that the results met 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.
- The early switch to an open-label trial limits any blinded assessment of long-term safety outcomes. Nonetheless, both the unblinded phase and the open-label extension are expected to provide additional important safety data.
- Inadequate adherence among participants appeared to drive the incident HIV infections in the TDF-FTC group, which led to the superior efficacy of CAB-LA as PrEP in the analysis.
- The trial conducted extensive baseline HIV testing, including the use of viral RNA, to ensure those enrolled were HIV negative. In addition, detection of HIV was delayed in several participants and a committee was available to advise sites on the use of sophisticated confirmatory testing methods. Similar testing resources are unlikely to be available in most real-world settings, raising concern over delayed diagnoses using conventional testing approaches.
- There were no incident infections in the tail phase during the period of cabotegravir decay after the last injection. However, given the risk of INSTI resistance, strategies to reduce incident infections and the time from infection to diagnosis during the tail phase will be important in real-world implementation.
- While this study was limited to women aged 18 years and older, studies to assess the safety and acceptability of cabotegravir in adolescents younger than 18 years and who weigh at least 35 kg are currently under evaluation (NCT04692077 and NCT04824131).
- Despite limiting enrollment to women using long-acting reversible contraception, 49 pregnancies were confirmed during the study. None of the pregnancies were associated with neural tube defects or other congenital anomalies, however, more safety data are needed before recommending the use of cabotegravir during pregnancy and breastfeeding.

Implications

The phase 3, multicenter, double-blind, randomized controlled HPTN 084 trial found injectable intramuscular CAB-LA to be superior to daily oral PrEP in preventing incident HIV infections in women in sub-Saharan Africa. This long-acting form of PrEP helps to overcome adherence challenges that are common with daily PrEP use and results from this trial informed the US Food and Drug Administration's approval of CAB-LA as PrEP in 2021.[1] Integrating injectable CAB-LA into existing HIV prevention programs brings several implementation considerations, especially in

resource-limited settings. 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.

References

1. U.S. Food & Drug Administration News Release. FDA Approves First Injectable Treatment for HIV Pre-Exposure Prevention, December 20, 2021. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-injectable-treatment-hiv-pre-exposure-prevention

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.