ICAP Journal Club

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Article

Kelley CF, Acevedo-Quiñones M, Agwu AL, et al for the PURPOSE 2 Study Team. Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons. *N Engl J Med*. Published online November 27, 2024. https://doi.org/10.1056/NEJMoa2411858

Study Summary

This phase 3, multi-center, double-blind, randomized, active-controlled trial (PURPOSE 2) evaluated the safety and efficacy of twice-yearly subcutaneous lenacapavir as pre-exposure prophylaxis (PrEP) for prevention of HIV infection in cisgender gay, bisexual, and other men, transgender women, transgender men, and gender nonbinary persons who have sex with partners assigned male at birth.

Study Setting

- Ninety-two trial sites in areas with evidence of substantial ongoing HIV transmission among cisgender men or transgender women: 61 sites in the United States, 9 in Brazil, 7 in Thailand, 6 in South Africa, 5 in Peru, 3 in Argentina, and 1 in Mexico.

Methods

- Eligible participants were cisgender gay, bisexual, and other men, transgender women, transgender men, and gender nonbinary persons who have condomless receptive anal sex with partners assigned male at birth; were at least 16 years of age; had unknown HIV status; and reported no HIV testing or PrEP use in the prior 3 months.
- Because of the high prevalence of testosterone (a teratogen) use among transgender men, participants assigned female at birth who engaged in frontal (vaginal) sex and who had the ability to become pregnant were required to use contraception.
- A cross-sectional incidence cohort was recruited to establish background HIV incidence. Participants in this cohort who received a diagnosis of HIV infection were referred for local HIV care, and HIV-negative participants were randomly assigned in a 2:1 ratio to receive subcutaneous lenacapavir or daily oral emtricitabine-tenofovir disoproxil fumarate (F/TDF).
- All participants underwent HIV testing with a rapid, point-of-care fourth-generation antigen-antibody test, a central laboratory fourth generation antigen–antibody test that was reflexively confirmed by an antibody assay if positive, and an HIV RNA test. HIV-positive samples were evaluated for recent HIV infection with the limiting antigen antibody avidity assay (LAg-EIA).

- Participants in the lenacapavir group received loading doses of two 300-mg tablets of lenacapavir on each of days 1 and 2, followed by subcutaneous lenacapavir (927 mg, as two 1.5-ml injections in the abdomen) every 26 weeks (within a window of ±7 days), and placebo tablets matching F/TDF.
- Participants in the F/TDF group received daily oral F/TDF (200 mg of emtricitabine and 300 mg of TDF) and placebo oral loading doses and injections matching lenacapavir.
- All the participants and personnel involved in the conduct of the trial were blinded to trial-group assignments except for the personnel who prepared or administered the injections.
- Randomly assigned participants were seen for follow-up at weeks 4, 8, and 13 and every 13 weeks thereafter.
- At each visit participants received:
    - HIV testing with both rapid point-of-care and central laboratory fourth-generation antigen–antibody testing, which if positive was confirmed with reflexive HIV-1 and HIV-2 differentiation antibody assay testing and qualitative HIV-1 RNA testing if antigen-antibody and antibody differentiation results were discrepant.
    - Safety laboratory testing and pregnancy testing (for participants assigned female at birth)
    - Drug adherence and HIV prevention counseling, including provision of male and female condoms and lubricant.
    - Evaluation of intimate partner violence and social harm from trial participation with appropriate referrals for support and counseling.
- At baseline and every 13 weeks thereafter, oropharyngeal and rectal swabs and urine samples were obtained for testing for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, as were blood samples for syphilis testing. Treatment of sexually transmitted infections was provided according to local guidelines.
- Adherence to lenacapavir was defined as on-time injection (within 28 weeks after the last injection).
    - HIV-negative participants who resumed the injection regimen more than 28 weeks after their previous injection received reloading with oral lenacapavir or placebo, following the same regimen used on days 1 and 2.
- Adherence in the F/TDF group was categorized as low (<2 tablets/week), medium (2-3 tablets/week), or high (≥4 tablets/week) on the basis of tenofovir diphosphate concentrations in dried-blood-spot samples obtained at all trial visits in a randomly selected representative sample of 10% of participants.
- The primary efficacy end point was incident HIV infection among randomly assigned participants, using a modified intention-to-treat approach that excluded participants who were adjudicated to have had HIV infection on the date of randomization.
    - The primary efficacy analysis assessed the incidence rate ratio (IRR) comparing HIV incidence among participants assigned to receive lenacapavir with the background HIV incidence.
    - The secondary efficacy analysis assessed the IRR comparing HIV incidence among participants assigned to receive lenacapavir with those assigned to receive F/TDF.

- Safety end points were adverse events and clinical laboratory abnormalities that occurred in participants who had received at least one dose of a trial drug or placebo.
- Based on a planned interim efficacy analysis, an external independent data monitoring committee concluded that the prespecified efficacy criteria for stopping the randomized, blinded phase of the trial had been met and the study was converted to an open-label trial. According to the trial protocol, the interim analysis became the primary analysis.

Study Population and Follow-up

- From June 2021 to December 2023, a total of 4,807 participants underwent screening; 378 of 4,634 with available HIV testing results received a diagnosis of HIV infection (8.2%), of whom 45 (11.9%) were categorized as having recently acquired HIV infection. The background incidence of HIV infection in the screened population was 2.37 per 100 person-years (95% confidence interval [CI], 1.65 to 3.42).
- A total of 3,265 participants were included in the modified intention-to treat efficacy analysis: 2,179 in the lenacapavir group and 1,086 in the F/TDF group.
- Baseline characteristics in the two trial groups were similar, and characteristics in the randomized population were similar to those in the screened population.
- The median age was 29 years (range 17 to 74); 98.0% were assigned male at birth, and 22.3% identified as gender diverse (14.6% as transgender women, 6.1% as gender nonbinary, and 1.3% as transgender men). Most participants identified as non-White (67.3%), including 37.7% who identified as Black, 12.7% as Asian and total of 62.8% of the participants were Hispanic or Latine.
- More than one quarter (26.8%) reported use of drugs with sex and laboratory-diagnosed sexually transmitted infections were common at baseline.
- A total of 3,220 participants had at least one post-randomization visit that included an HIV test, for a total of 2,905 person-years of follow-up accrued for the assessment of incident HIV infection.
- Overall trial retention was 94.4% at week 26, 93.3% at week 52 and 91.3% at week 104; retention was similar in the two groups.
- Injections were administered on time for 91.0% of participants at week 26 and 92.8% at week 52; percentages were similar between the two groups.
- Tenofovir diphosphate concentrations consistent with high adherence were seen in 82% of participants at week 8, 67% at week 26, and 62% at week 52.

Efficacy Outcomes

- A total of 11 incident HIV infections were observed: in two participants in the lenacapavir group (0.10 per 100 person-years; 95% CI, 0.01 to 0.37) and in nine participants in the F/TDF group (0.93 per 100 person-years; 95% CI, 0.43 to 1.77).
- HIV incidence with lenacapavir was 96% lower than the background incidence (IRR 0.04; 95% CI, 0.01 to 0.18; $p<0.001$), and 89% lower than with F/TDF (IRR 0.11; 95% CI, 0.02 to 0.51; $p=0.002$).

- The two participants in the lenacapavir group who acquired HIV infection had lenacapavir concentrations within the expected protective range. In one participant, retrospective testing first detected HIV-1 RNA at week 8 and the participant was diagnosed at week 13. The other participant was diagnosed at week 26, with no evidence of a delayed diagnosis. Both participants had the N74D capsid resistance mutation found at their HIV diagnosis visit and neither participant reported symptoms of HIV seroconversion.
- All nine participants in the F/TDF group who received a diagnosis of HIV had evidence of low or no adherence or had discontinued F/TDF more than 10 days before diagnosis.

<u>Safety Outcomes</u>

- The most common adverse events were injection-site reactions, occurring in 83.2% of participants in the lenacapavir group and in 69.5% given the placebo injection.
- A total of 26 participants (1.2%) in the lenacapavir group and 3 (0.3%) in the F/TDF group discontinued the trial regimen because of injection-site reactions.
- Most injection-site reactions were grade 1 or grade 2 in severity, and the frequency and severity of injection-site reactions diminished with subsequent injections.
- Sub-cutaneous nodules, pain, and erythema were the most commonly reported injection-site reactions in both groups. Keloid formation was not reported.
    - Subcutaneous nodules occurred more frequently in the lenacapavir group than in the F/TDF group (63.4% vs. 39.2%).
    - The median duration of injection-site nodules was 183 days (interquartile range [IQR] 89 to 274) in the lenacapavir group and 64 days (IQR 19 to 98) in the F/TDF group.
    - The median duration of induration was 84 days (IQR 8 to 190) in the lenacapavir group and 8 days (IQR 5 to 57) in the F/TDF group.
    - The median diameter of the largest nodule per participant was 3.0 cm (IQR 2.0 to 4.0) in the lenacapavir group and 2.0 cm (IQR 1.0 to 2.5) in the F/TDF group.
    - The incidence of pain in the lenacapavir group was similar to that in the F/TDF group (56.4% vs. 53.4%).
- The most common adverse events, aside from injection-site reactions, were rectal chlamydia infection (13.2% in the lenacapavir group, 11.8% in the F/TDF group), oropharyngeal gonococcal infection (13.0% in the lenacapavir group, 10.9% in the F/TDF group), and rectal gonococcal infection (10.7% in the lenacapavir group, 9.1% in the F/TDF group).
- Overall, the incidence of adverse events was similar in the two groups with respect to grade 2 or higher adverse events (53.7% in the lenacapavir group, 54.6% in the F/TDF group), grade 3 or higher adverse events (4.2% in the lenacapavir group, 6.0% in the F/TDF group), serious adverse events (3.3% in the lenacapavir group, 4.0% in the F/TDF group), and discontinuations due to adverse events (0.3% in the lenacapavir group, 0.6% in the F/TDF group).

- Laboratory abnormalities occurred in 84.6% of participants in the lenacapavir group and in 87.5% of the participants in the F/TDF group. Most were grade 1 or 2 in severity and occurred in similar frequencies in the two groups, except for more frequent occurrence of decreased creatinine clearance in the F/TDF group (p=0.002).
- No participant became pregnant and there were six deaths (four in the lenacapavir group and two in the F/TDF group), none of which were assessed to be related to a trial drug.

Critical Analysis

The phase 3, multi-center, double-blind, randomized, active-controlled PURPOSE 2 trial found twice-yearly subcutaneous lenacapavir to be highly efficacious as PrEP in men and gender-diverse persons who have sex with men. In addition, lenacapavir was more efficacious than daily oral F/TDF in preventing HIV infection and safety outcomes were similar between the groups, other than injection site reactions, which were more common in the lenacapavir group.

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

- Background incidence was estimated using a cross-sectional cohort, whereas the study group incidence was determined prospectively. This trial design was used because comparison to incidence rates in a placebo group is considered unethical given current recommendations for PrEP in these at-risk populations.
- Lenacapavir is a capsid inhibitor drug, and there is no evidence of circulating N74D capsid resistance mutation in any population. This suggests that the two cases of HIV infection in the lenacapavir group, with emergence of capsid resistance, resulted from lenacapavir monotherapy.
- There was no evidence of delayed HIV seroconversion or delayed diagnosis, which contrasts with the findings from cabotegravir studies. However, with only two seroconversion cases, more data are needed, and the open-label extension phase of this trial may provide further insights.
- Although injection-site reactions with lenacapavir were relatively common and expected, discontinuations of the drug were rare (<2%). The occurrence of injection-site reactions decreased with subsequent doses, which is a phenomenon that has been observed with lenacapavir in other contexts. The authors hypothesize that this was in part due to increased clinical experience with lenacapavir injections, with improvement in pre-injection counseling on what to expect, injection techniques and pain mitigation efforts.
- Lenacapavir was found to have superior efficacy to F/TDF as PrEP, even in the context of relatively high adherence to daily oral PrEP. However, oral adherence did decline over time, and the breakthrough infections in the F/TDF group were associated with low adherence to F/TDF.

Implications

The PURPOSE 2 trial found twice-yearly subcutaneous lenacapavir was highly efficacious as PrEP among men and gender-diverse persons. The efficacy and safety profiles of lenacapavir were consistent with previous results among cisgender women in PURPOSE 1.[1] Taken together, these findings suggest that lenacapavir is an important new option for PrEP, and its long-acting and discreet nature has the ability to overcome many barriers to effective PrEP use. Lenacapavir, therefore, has the potential to make a substantial impact on global HIV prevention efforts if it is affordable and made accessible to the most at-risk populations.

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.

Reference

1. Bekker L, Das M, Abdool Karim Q, et al. for the PURPOSE I Study Team. Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women. *N Engl J Med*. 2024;391(13):1179–1192.