ORIGINAL ARTICLE

Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons

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ABSTRACT

BACKGROUND

Twice-yearly subcutaneous lenacapavir has been shown to be efficacious for prevention of HIV infection in cisgender women. The efficacy of lenacapavir for preexposure prophylaxis (PrEP) in cisgender men, transgender women, transgender men, and gender-nonbinary persons is unclear.

METHODS

In this phase 3, double-blind, randomized, active-controlled trial, we randomly assigned participants in a 2:1 ratio to receive subcutaneous lenacapavir every 26 weeks or daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF). The primary efficacy analysis compared the incidence of HIV infection in the lenacapavir group with the background HIV incidence in the screened population. The secondary efficacy analysis compared the incidence of HIV infection in the lenacapavir group with that in the F/TDF group.

RESULTS

Among 3265 participants who were included in the modified intention-to-treat analysis, HIV infections occurred in 2 participants in the lenacapavir group (0.10 per 100 person-years; 95% confidence interval [CI], 0.01 to 0.37) and in 9 participants in the F/TDF group (0.93 per 100 person-years; 95% CI, 0.43 to 1.77). The background HIV incidence in the screened population (4634 participants) was 2.37 per 100 person-years (95% CI, 1.65 to 3.42). The incidence of HIV infection in the lenacapavir group was significantly lower than both the background incidence (incidence rate ratio, 0.04; 95% CI, 0.01 to 0.18; P<0.001) and the incidence in the F/TDF group (incidence rate ratio, 0.11; 95% CI, 0.02 to 0.51; P=0.002). No safety concerns were identified. A total of 26 of 2183 participants (1.2%) in the lenacapavir group and 3 of 1088 (0.3%) in the F/TDF group discontinued the trial regimen because of injection-site reactions.

CONCLUSIONS

The HIV incidence with twice-yearly lenacapavir was significantly lower than the background incidence and the incidence with F/TDF. (Funded by Gilead Sciences; PURPOSE 2 ClinicalTrials.gov number, NCT04925752.)

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The number of new human immunodeficiency virus (HIV) infections has declined by 35% globally since 2010; however, new diagnoses have increased among cisgender gay, bisexual, and other men who have sex with men and among transgender women, with intersectional disparities amplifying the burden among persons of color who are also gender diverse (transgender or nonbinary).[1,2] In 2022 in the United States, 67% of the new HIV diagnoses were among cisgender gay men, and more than 70% of the new diagnoses were among Black, Hispanic, or Latine persons.[2,3] Global preexposure prophylaxis (PrEP) use remains low — only 16.5% of the Joint United Nations Program on HIV/AIDS goal of 21.2 million users by 2025.[4] In populations that are most disproportionately affected by HIV, uptake of and adherence to PrEP is limited, which underscores the need to develop new PrEP options, especially longer-acting options that do not depend on daily oral adherence or frequent injection visits.[5-9]

Lenacapavir is a first-in-class, multistage HIV-1 capsid inhibitor that is highly potent and has a long half-life, allowing twice-yearly subcutaneous administration.[10-13] Lenacapavir has been shown to be efficacious for the prevention of HIV infection in cisgender women,[14] and capsid inhibitors, including lenacapavir, have shown preclinical efficacy in nonhuman primate rectal challenge models.[15,16] We evaluated the safety and efficacy of twice-yearly subcutaneous lenacapavir 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.

METHODS

TRIAL DESIGN

We conducted a phase 3, multicenter, double-blind, randomized trial (PURPOSE 2), in which participants were randomly assigned to receive lenacapavir or emtricitabine–tenofovir disoproxil fumarate (F/TDF) as an active internal control (the randomized cohort). The background incidence of HIV infection, the counterfactual control, was estimated in the screened population (the cross-sectional incidence cohort). The primary objective was to determine the efficacy of lenacapavir for prevention of HIV infection by comparing the incidence of HIV infection in the lenacapavir group with the background incidence in the cross-sectional incidence cohort (Fig. 1A and the Supplementary Methods section of the Supplementary Appendix, available with the full text of this article at NEJM.org). The secondary objective was to assess the incidence of HIV infection in the lenacapavir group as compared with that in the F/TDF group. This counterfactual background-HIV-incidence design for HIV PrEP clinical trials was developed through consensus among academic researchers, regulators, drug developers, and other stakeholders, allowing assessment of new PrEP agents without a placebo control.[14,17,18] We developed the trial protocol (available at NEJM.org) in collaboration with the PURPOSE 2 principal investigators and Global Community Advisory Group of PrEP community advocates.[19]

PARTICIPANTS AND PROCEDURES

We sought to recruit participants from demographic subpopulations that are disproportionately affected by HIV and have historically been underrepresented in HIV clinical trials.[20] Therefore, we selected 92 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.[9,21-23] 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 3 months before screening. We established trial-wide demographic-specific recruitment goals and created site-specific diversity plans with input from investigators and community members and based on local HIV epidemiologic data (see the Supplementary Appendix).[20]

During screening, all the participants underwent real-time HIV testing with a Food and Drug Administration (FDA)–approved, rapid, point-of-care fourth-generation antigen–antibody test; a fourth-generation antigen–antibody test performed by a central laboratory that, if positive, was confirmed by an antibody assay to differentiate between HIV-1 and HIV-2; and a qualitative HIV RNA test if the fourth-generation test and differentiation assay results were discrepant (Fig. S1 in the Supplementary Appendix). All the participants also

underwent testing with a quantitative HIV-1 RNA test (Cobas 6800 HIV-1 test [Roche]) during screening (lower limit of quantification, 20 copies per milliliter). We further tested HIV-positive samples for recent HIV infection with a limiting antigen antibody avidity assay (LAg-EIA, Sedia Biosciences) (Fig. S2 and Tables S1 and S2). Participants who received a diagnosis of HIV infection were referred for treatment.

Participants who were HIV-negative and met additional eligibility criteria underwent randomization, in a 2:1 ratio, to receive either subcutaneous lenacapavir (927 mg as two 1.5-ml injections in the abdomen every 26 weeks, within a window of ±7 days) or daily oral F/TDF (200 mg of emtricitabine and 300 mg of TDF). Participants in the lenacapavir group received placebo tablets matching F/TDF, and participants in the F/TDF group received placebo injections (polyethylene glycol 400) matching lenacapavir. Participants in the lenacapavir group received oral loading doses of two 300-mg tablets of lenacapavir each on days 1 and 2, and those in the F/TDF group received two oral placebo tablets matching lenacapavir. Randomization was centralized, not stratified, with a block size of six. Injections were prepared and administered by trial-site personnel. All the participants and trial personnel were unaware of the trial-group assignments, except for the personnel who prepared or administered the injections.

Participants were seen for follow-up at weeks 4, 8, and 13, and every 13 weeks thereafter. Rapid point-of-care and central-laboratory fourth-generation antigen–antibody testing was performed at each visit, with results available in real time. If central-laboratory fourth-generation antigen–antibody testing was positive, confirmatory testing was conducted in the same way as that at screening, described above. We conducted safety laboratory testing and pregnancy testing (among participants assigned female at birth), and archived blood samples at each visit. 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.

We conducted HIV prevention and drug adherence counseling at each visit and provided male and female condoms and lubricant. We assessed participants for intimate partner violence and social harm resulting from trial participation and provided referrals for support and counseling. Treatment of sexually transmitted infections was provided according to local guidelines. Participants with HIV infection received counseling and were referred for treatment. 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.

Adherence to lenacapavir was defined as on-time injection (within 28 weeks after the last injection). Participants who presented later than 28 weeks after their previous injection were required to repeat day 1 procedures for HIV testing and reloading with oral lenacapavir or placebo. Participants with a negative point-of-care HIV test could receive injections of the trial drug while the results of central antigen–antibody and quantitative HIV RNA testing were pending, at the investigator's discretion. Participants who chose to discontinue the trial drug were offered open-label daily F/TDF (or emtricitabine–tenofovir alafenamide fumarate [F/TAF] in the United States).

Between December 21, 2021, and May 16, 2022, the FDA placed a clinical hold on lenacapavir injections because of concerns regarding the incompatibility of lenacapavir with borosilicate glass vials.[24] Participants who were due for an injection received open-label daily F/TDF or F/TAF, or (after approval of a protocol amendment on January 31, 2022) weekly oral lenacapavir at a dose of 300 mg or matched placebo, according to the participant's original randomization assignment. After the hold was lifted, participants resumed the original trial regimen they were assigned.

END POINTS

The primary efficacy end point was new HIV infection among the participants who had undergone randomization. Positive HIV testing results were reviewed by an adjudication panel, whose members were unaware of the trial-group assignments, to determine HIV status and the earliest visit with evidence of HIV infection (see the Supplementary Appendix). Efficacy analyses used a modified intention-to-treat approach that excluded participants who were determined by the adjudication panel to have had HIV infection on the date of randomization. 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.

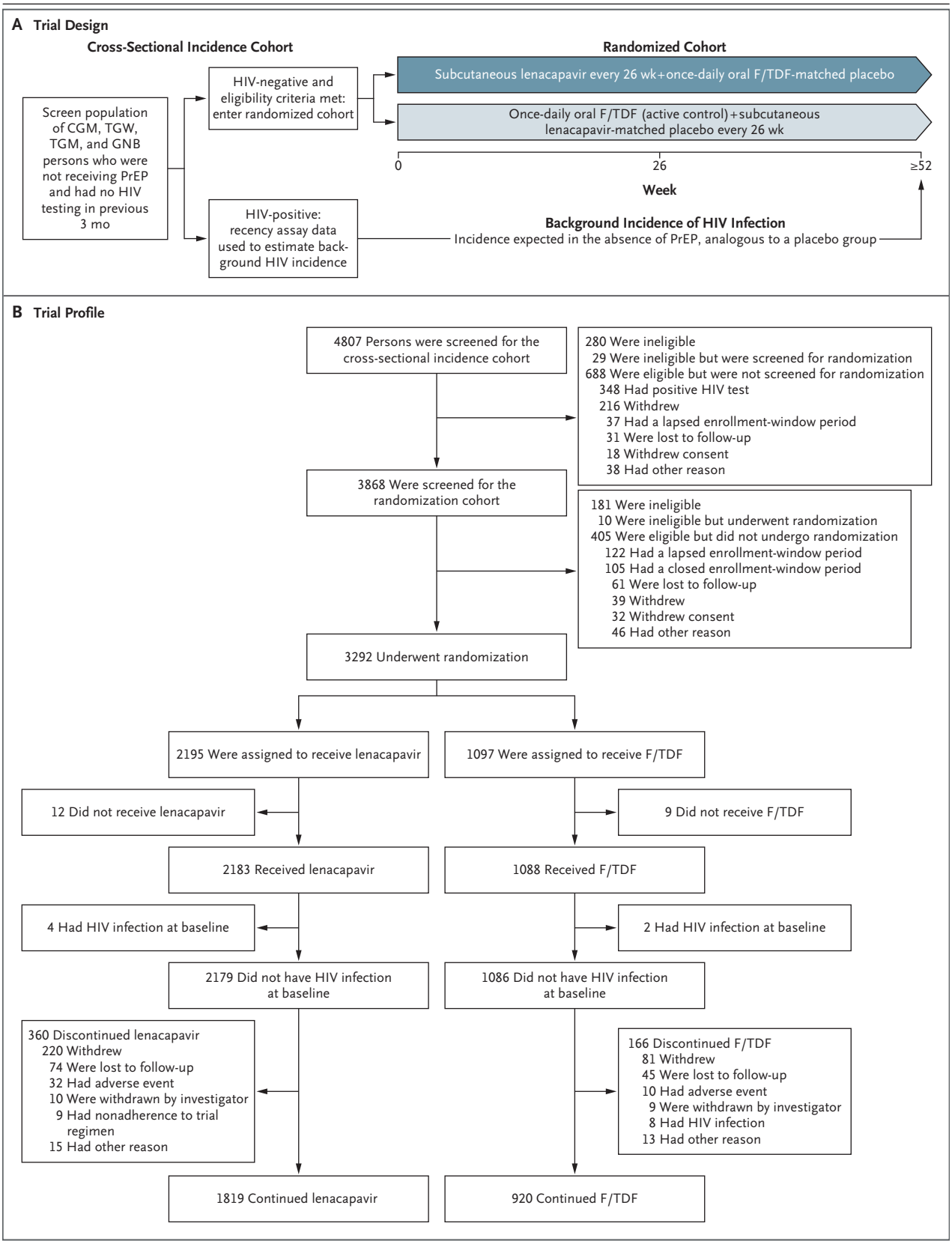


Figure 1 (facing page). Trial Design and Trial Profile.

Panel A shows the trial design. The trial began with a specialized screening process that allowed for the cross-sectional estimation of the background incidence of human immunodeficiency virus (HIV) infection among cisgender men (CGM), transgender women (TGW), transgender men (TGM), and gender-nonbinary (GNB) persons who have sex with partners assigned male at birth who were screened for the trial. Eligible participants (who had no HIV testing in the preceding 3 months, no use of preexposure prophylaxis [PrEP] in the preceding 3 months, and who were sexually active) underwent rapid and central-laboratory HIV testing. Those found to have HIV infection underwent additional testing with an assay that assessed the recency of HIV infection. Participants with HIV infection were referred for care, and their participation in the trial ended. Of the 4807 participants who were screened for the cross-sectional incidence cohort, 4634 had a nonmissing result of a central laboratory HIV test (including those who subsequently underwent randomization); these participants contributed to the estimation of the background incidence of HIV infection, which was derived from their HIV test and recency assay results with the use of a recent infection testing algorithm. The background incidence was a cross-sectional estimate derived during the screening period; there was no longitudinal follow-up for the background incidence estimate. Participants who were included in the cross-sectional cohort could then proceed to the randomized portion of the trial if they did not have HIV infection and were otherwise eligible (including having a body weight of ≥35 kg and an estimated glomerular filtration rate of ≥60 ml per minute). These participants were randomly assigned in a 2:1 ratio to receive lenacapavir or emtricitabine–tenofovir disoproxil fumarate (F/TDF), along with the corresponding matched placebo (oral placebo tablets in the lenacapavir group and placebo injection in the F/TDF group). The first participant was screened in June 2021, the 50th percentile participant underwent randomization in August 2023, and the last participant underwent randomization in December 2023. Panel B shows the trial profile. Of note, 29 of the participants who were screened for the cross-sectional incidence cohort were screened for randomization despite being ineligible. Therefore, 251 ineligible participants did not proceed to the randomization screening, in addition to 688 participants who were eligible but did not proceed to the randomization screening. Similarly, 10 of the participants who were screened for the randomization cohort were ineligible but nevertheless underwent randomization. Overall, trial retention and the proportion of participants who continued the trial regimen in a blinded manner were similar in the two groups, with the exception of acquisition of HIV infection, which was lower in the lenacapavir group than in the F/TDF group.

TRIAL OVERSIGHT

The trial was approved by the regulatory authorities in each country and the appropriate institutional review board or ethics committees at each site and was conducted in compliance with Good Clinical Practice and Good Participatory Practice Guidelines.[25] All the participants provided written informed consent; participants who were younger than 18 years of age provided assent along with parental or guardian consent. The sponsor (Gilead Sciences) collected the data, monitored the conduct of the trial, and performed the statistical analyses. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Editorial assistance was funded by the sponsor and was performed in accordance with Good Publication Practice guidelines.

On September 11, 2024, an external independent data monitoring committee reviewed the interim efficacy analysis and concluded that the prespecified efficacy criteria for stopping the randomized, blinded phase of the trial had been met. According to the trial protocol, the interim analysis became the primary analysis. Participants began to be made aware of the trial-group assignments and were offered the option to receive lenacapavir in an open-label fashion on September 25, 2024.

STATISTICAL ANALYSIS

We calculated the background incidence of HIV infection in the screening cohort with the use of a recent infection testing algorithm, a method extensively used for HIV incidence rate estimation in epidemiologic surveillance.[26,27] In brief, screened participants could contribute to the cross-sectional incidence cohort if they met eligibility criteria pertaining to gender, age, sexual behaviors, recent PrEP use, and recent HIV testing. Those found to have HIV infection during screening underwent additional recent infection testing with a limiting antigen antibody avidity assay (Sedia Biosciences)[28] and viral-load testing (Fig. S2 and Tables S1 and S2). The HIV testing and recent infection data were incorporated into the recent infection testing algorithm, which used empirically determined assay parameters (see the Supplementary Methods section in the Supplementary Appendix)[26] to generate an estimate of the background incidence within the screened population.

The primary efficacy analysis assessed the incidence rate ratio for the comparison of the incidence of HIV infection in the lenacapavir group with the background incidence (with the use of the Wald test).[27] The secondary efficacy analysis assessed the incidence rate ratio for the comparison of the incidence of HIV infection in the lenacapavir group with that in the F/TDF group (with the use of Poisson regression). We estimated that a sample of 3000 participants (randomly assigned in a 2:1 ratio to the lenacapavir group and the F/TDF group) would provide the trial with more than 95% power to show an incidence of HIV infection that was at least 20% lower in the lenacapavir group than the background incidence, assuming a background incidence of at least 3 per 100 person-years (Table S3). An interim analysis was planned to occur when 50% of the 3000 participants (target enrollment), or 1500 participants, had completed at least 52 weeks of follow-up or had permanently withdrawn from the randomized, blinded trial (52 weeks after random assignment of the 1500th participant). We tested the prespecified efficacy hypotheses with the use of a gated fixed-sequence approach with a one-sided alpha level of 0.0026, the prespecified interim alpha spending of the total alpha of 0.025 (one-sided) for the trial. The prespecified order of hypotheses testing started with testing whether the incidence of HIV infection in the lenacapavir group was significantly lower than the background incidence, followed by testing whether lenacapavir was superior to F/TDF (Table S4).

A randomly preselected, representative sample of 10% of the participants was chosen for evaluation of lenacapavir concentrations to understand lenacapavir exposure and for evaluation of adherence to F/TDF (the pharmacokinetics cohort). Lenacapavir plasma concentrations were quantified with the use of a validated high-performance liquid chromatography–tandem mass spectrometry method (calibrated range of 0.5 to 500 ng per milliliter or 0.1 to 100 ng per milliliter) and plotted with R software, version 4.3.1 (R Foundation for Statistical Computing).[12] Adherence in the F/TDF group was categorized as low (<two tablets per week), medium (two or three tablets per week), or high (≥four tablets per week) on the basis of tenofovir diphosphate concentrations in dried-blood-spot samples obtained at all trial visits.[29,30] Lenacapavir plasma concentrations were assessed in the case of new HIV infections and compared with concentrations associated with antiviral efficacy, the inhibitory quotient (IQ; defined as the protein-adjusted 95% effective concentration in MT-4 cells), and four times the protein-adjusted 95% effective concentration in vitro (IQ4).[31] Genotypic HIV resistance testing of the capsid region of the *gag* gene and protease and reverse transcriptase regions of the *pol* gene was performed in participants who acquired HIV infection (Monogram Biosciences). HIV-1 RNA single-copy assay was also performed retrospectively on samples that were obtained before diagnosis of HIV-1 infection (Accelevir Diagnostics).[32]

Adverse events, including injection-site reactions and laboratory abnormalities, were descriptively summarized. All the analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS AND BACKGROUND INCIDENCE OF HIV INFECTION

From June 28, 2021, to December 12, 2023, a total of 4807 participants underwent screening, and 4634 had available results from HIV testing. Of these participants, 378 (8.2%) received a diagnosis of HIV infection at screening, 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) (Fig. 2A). A total of 3271 screened participants who had negative HIV tests underwent randomization and received at least one dose of a trial drug: 2183 in the lenacapavir group and 1088 in the F/TDF group (Fig. 1B). Six participants received a diagnosis of HIV infection on day 1 and were excluded from the modified intention-to-treat analysis (4 in the lenacapavir group and 2 in the F/TDF group) (Table S5). The median age was 29 years (range, 17 to 74), and 33.5% were 25 years of age or younger; 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) (Table 1). Overall, most participants identified as non-White (67.3%), including 37.7% who identified as Black and 12.7% as Asian. A total of 62.8% of the participants were Hispanic or Latine. In the United States, 50.2% were non-

White, and 32.6% were Hispanic or Latine. More than one quarter (26.8%) reported use of drugs with sex. Laboratory-diagnosed sexually transmitted infections were common at baseline. The baseline characteristics in the two trial groups were similar, and the characteristics in the randomized population were similar to those in the screened population (Table S6).

FOLLOW-UP AND ADHERENCE

A total of 3220 participants had at least one postrandomization visit that included an HIV test, for a total of 2905 person-years of follow-up accrued for the assessment of new HIV infection. The overall trial retention at week 26 was 94.4% (2834 of 3001 participants), at week 52 was 93.3% (1191 of 1277 participants), and at week 104 was 91.3% (63 of 69 participants); trial retention was similar in the two trial groups (Table S7). Overall adherence to lenacapavir or placebo injection was similar in the two groups (administered on time in 2606 of 2864 participants [91.0%] at week 26 and in 1016 of 1095 [92.8%] at week 52) (Fig. 3A and Table S8). Tenofovir diphosphate concentrations consistent with high adherence (≥four tablets per week) were seen in 82% of the participants at week 8, in 67% at week 26, and in 62% at week 52 (Fig. 3B). Of 163 participants who had undergone randomization before the clinical hold, none acquired HIV infection (Table S9). More than one third of the participants in each group (36.8% [771 of 2096 participants] in the lenacapavir group and 34.2% [354 of 1036 participants] in the F/TDF group) had laboratory-diagnosed sexually transmitted infections; the incidence was similar in the two groups (Tables S10 and S11).

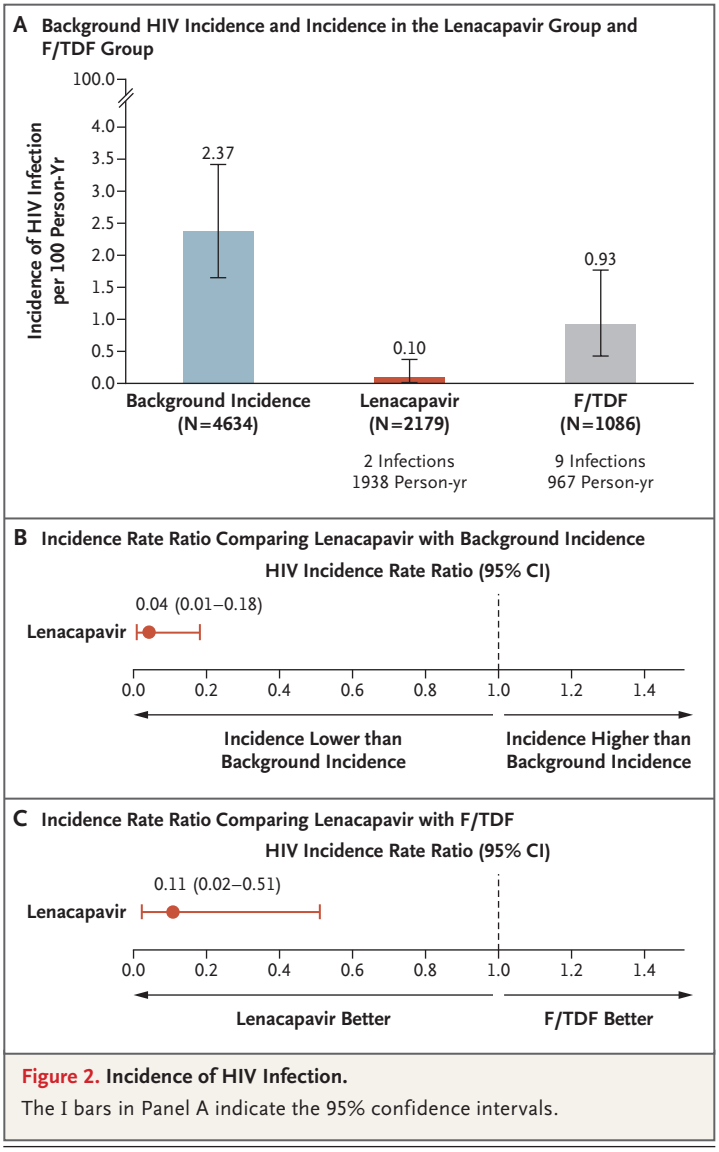


Figure 2. Incidence of HIV Infection.
The I bars in Panel A indicate the 95% confidence intervals.

EFFICACY

A total of 11 new 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). The incidence of HIV infection with lenacapavir was 96% lower than the background incidence (incidence rate ratio, 0.04; 95% CI, 0.01 to 0.18; P<0.001) (Fig. 2B), and the incidence with lenacapavir was 89% lower than that with F/TDF (incidence rate ratio, 0.11; 95% CI, 0.02 to 0.51; P=0.002) (Fig. 2C and Fig. S3).

Among 2179 participants in the lenacapavir group, 2 participants acquired HIV infection; lenacapavir concentrations for these 2 participants and the pharmacokinetics cohort and results of HIV testing are shown in Figure 3A and Table S12. Participant A was a transgender woman, with latent syphilis that was diagnosed and treated at baseline, who engaged in transactional sex and who received a diagnosis of HIV infection at the week 13 visit. Participant B was a cisgender gay man with a diagnosis of rectal chlamydia that was treated at screening and who received a diagnosis of HIV infection at week 26. The lenacapavir concentrations in both participants were within the range of the overall lenacapavir concentrations in the pharmacokinetics cohort, which were also similar to those in previous studies.[34]

Retrospective standard HIV-1 RNA viral-load testing of samples obtained at previous visits did not reveal delayed diagnosis for either participant. HIV-1 RNA single-copy testing, performed retrospectively for previous visits, including at baseline, was positive only for Participant A at week 8 (4.8 copies per milliliter) (Fig. 3A). Both participants had the N74D capsid resistance mutation found at their HIV diagnosis visit.[10,35] Neither participant reported symptoms of HIV seroconversion.

All nine participants in the F/TDF group who received a diagnosis of HIV infection had evidence of low or no adherence or had discontinued F/TDF more than 10 days before diagnosis. Of the nine participants, eight had available

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Lenacapavir (N=2183)	F/TDF (N=1088)
Age		
Median (range) — yr	28 (17–74)	29 (17–73)
16 to ≤25 yr — no. (%)	752 (34.4)	344 (31.6)
Country — no. (%)		
Argentina	161 (7.4)	64 (5.9)
Brazil	769 (35.2)	396 (36.4)
Mexico	8 (0.4)	4 (0.4)
Peru	309 (14.2)	138 (12.7)
South Africa	246 (11.3)	112 (10.3)
Thailand	250 (11.5)	139 (12.8)
United States	440 (20.2)	235 (21.6)
Race or ethnic group — no./total no. (%)†		
Asian	269/2175 (12.4)	144/1086 (13.3)
Black	811/2175 (37.3)	420/1086 (38.7)
Indigenous or Indigenous ancestry	341/2175 (15.7)	156/1086 (14.4)
White	722/2175 (33.2)	344/1086 (31.7)
Other and other multiracial	32/2175 (1.5)	22/1086 (2.0)
Hispanic or Latine	1378/2182 (63.2)	675/1088 (62.0)
Gender identity — no. (%)		
Cisgender man	1697 (77.7)	846 (77.8)
Transgender woman	315 (14.4)	161 (14.8)
Transgender man	29 (1.3)	14 (1.3)
Gender nonbinary‡	136 (6.2)	63 (5.8)
Other§	6 (0.3)	4 (0.4)
Sexual orientation — no./total no. (%)		
Straight or heterosexual	148/2168 (6.8)	66/1079 (6.1)
Gay	1634/2168 (75.4)	806/1079 (74.7)
Bisexual	322/2168 (14.9)	166/1079 (15.4)
Other¶	64/2168 (3.0)	41/1079 (3.8)
No previous HIV testing — no. (%)	597 (27.3)	306 (28.1)
Median time since last HIV test (range) — mo‖	7.2 (2.6–149.4)	7.1 (1.2–274.2)
Any previous use of PrEP — no. (%)	515 (23.6)	249 (22.9)
Median time since last use of PrEP (range) — mo**	13.0 (0.7–103.9)	10.8 (0.7–274.5)

Table 1. (Continued.)

Characteristic	Lenacapavir (N = 2183)	F/TDF (N = 1088)
Condomless receptive anal sex with ≥2 partners in previous 12 wk — no. (%)	2128 (97.5)	1049 (96.4)
Participant-reported use of stimulants with sex in previous 12 wk — no. (%)	491 (22.5)	271 (24.9)
Some college or university degree — no./total no. (%)	1105/2182 (50.6)	574/1086 (52.9)
Sexually transmitted infection — no. (%)††		
Chlamydia trachomatis	253 (11.6)	126 (11.6)
Neisseria gonorrhoeae	193 (8.8)	115 (10.6)
Syphilis	84 (3.8)	43 (4.0)
Use of gender-affirming hormone therapy — no. (%)‡‡	253 (11.6)	131 (12.0)

* F/TDF denotes emtricitabine–tenofovir disoproxil fumarate, HIV human immunodeficiency virus, and PrEP preexposure prophylaxis.

† Race and ethnic group were reported by the participants. The "Black" category included all the participants who identified as being Black or as being of Black ancestry and included the terms "Black," "Black/White," "Black/Pardo" (Brazilian term for a specific racial category), "Black/Brown" (Brazil), "Black/Colored" (South African term for a specific racial category), "Black/American Indian or Alaska Native," "Black/Asian," and "Black/Native Hawaiian or Pacific Islander." The "Indigenous or Indigenous ancestry" category included the terms "American Indian or Alaska Native," "Native Hawaiian or Pacific Islander," "Asian/Native Hawaiian or Pacific Islander," "White/Native Hawaiian or Pacific Islander," and "White/American Indian or Alaskan Native." The "other and other multiracial" category included the terms "Asian/White," "Colored" (South Africa), "Pardo" (Brazil), "White/Brown" (Brazil), "multiracial any other," and "not multiracial other."

‡ Among the participants who identified as gender nonbinary, 122 (89.7%) in the lenacapavir group and 53 (84.1%) in the F/TDF group were assigned male at birth.

§ The "other" category included participants who identified as "Travesti" (3 participants in the lenacapavir group and 3 in the F/TDF group) or as an "other" gender (3 in the lenacapavir group and 1 in the F/TDF group).

¶ The "other" category included the terms "pansexual" (46 participants in the lenacapavir group and 26 in the F/TDF group), "queer" (10 in the lenacapavir group and 12 in the F/TDF group), "homosexual" (3 in the lenacapavir group and 3 in the F/TDF group), "lesbian" (2 in the lenacapavir group and none in the F/TDF group), and "any other" (3 in the lenacapavir group and none in the F/TDF group).

‖ Data are included for 1585 participants in the lenacapavir group and 782 in the F/TDF group.

** Included are participants who were not taking PrEP at baseline (449 in the lenacapavir group and 215 in the F/TDF group).

†† *Chlamydia trachomatis* and *Neisseria gonorrhea* diagnoses were based on testing of pharyngeal, rectal, and urethral (urine) samples, performed by central and local laboratories. Blood testing for syphilis was performed locally with the use of local testing protocols.

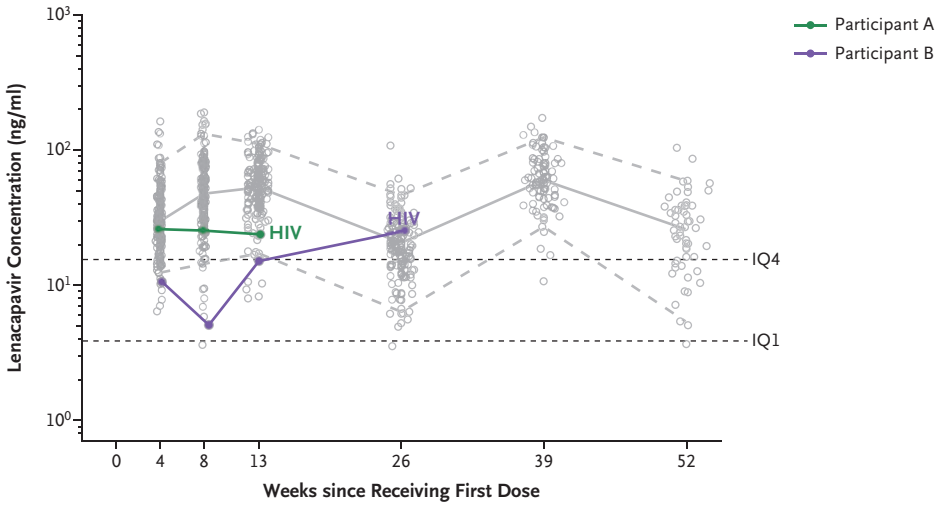
‡‡ Use of gender-affirming hormone therapy included concomitant use with the trial regimen during the randomized, blinded phase.

dried-blood-spot samples for analysis of tenofovir diphosphate concentrations. Of those eight participants, two had low concentrations and six had concentrations below the quantification limit. The one participant who was missing a dried-blood-spot sample had discontinued F/TDF (Fig. 3B). One participant was found to have an emtricitabine resistance mutation (M184V).[36]

SAFETY

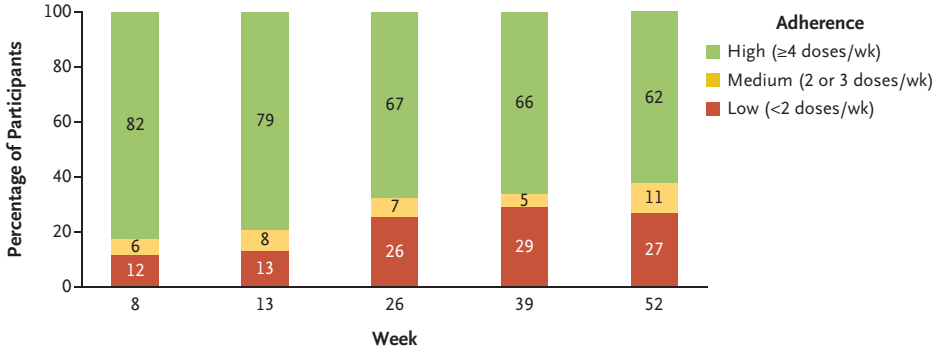
Excluding injection-site reactions, the three most common adverse events were rectal chlamydia infection (in 289 participants [13.2%] in the lenacapavir group and in 128 [11.8%] in the F/TDF group), oropharyngeal gonococcal infection (in 283 [13.0%] in the lenacapavir group and in 119 [10.9%] in the F/TDF group), and rectal gonococcal infection (in 233 [10.7%] in the lenacapavir group and in 99 [9.1%] in the F/TDF group) (Table 2). Overall, the incidence of adverse events was similar in the two groups with respect to grade 2 or higher adverse events (in 1173 [53.7%] in the lenacapavir group and in 594 [54.6%] in the F/TDF group), grade 3 or higher adverse events (in 91 [4.2%] in the lenacapavir group and in 65 [6.0%] in the F/TDF group) (Table S13), serious adverse

A Lenacapavir Plasma Concentrations in the Pharmacokinetics Cohort and in the Two Participants in the Lenacapavir Group Who Acquired HIV Infection



No. in Pharmacokinetics Cohort	159	149	170	157	88	56

B Adherence in the F/TDF Group



No. of Participants	102	100	98	65	37

events (in 71 [3.3%] in the lenacapavir group and in 43 [4.0%] in the F/TDF group), and discontinuations due to adverse events (in 7 [0.3%] in the lenacapavir group and in 7 [0.6%] in the F/TDF group) (Table S14). There were six deaths (four in the lenacapavir group and two in the F/TDF group); none were assessed by the investigator as being related to a trial drug. No participant became pregnant.

Laboratory abnormalities occurred in 84.6% of the participants in the lenacapavir group and in 87.5% of those in the F/TDF group; most were grade 1 or 2 in severity and occurred in similar frequencies in the two trial groups, except for more frequent occurrence of decreased creatinine clearance in the F/TDF group. A notable difference between the groups in laboratory measures was the median change from baseline in estimated glomerular filtration rate according to the Cockcroft–Gault formula: at week 26, there was a slight increase in the lenacapavir group (+1.2 ml per minute [interquartile range, –8.0 to 10.9]) and a decline in the F/TDF group (–3.0 ml per minute [interquartile range, –12.4 to 6.5]) (P<0.001); at week 52, there was an increase in the lenacapavir group (+0.6 ml per minute [interquartile range, –10.3 to 10.8]) and a decline in the F/TDF group (–2.9 ml per minute [interquartile range, –13.8 to 7.4]) (P=0.002). Grade 3 and 4 laboratory abnormalities occurred in 243 of 2153 participants

Figure 3 (facing page). Lenacapavir Plasma Concentrations and Adherence to F/TDF.

A randomly preselected, representative sample of 10% of the participants was chosen for evaluation of lenacapavir concentrations to understand lenacapavir exposure and for evaluation of adherence to F/TDF (the pharmacokinetics cohort). Panel A shows the lenacapavir plasma concentrations in the pharmacokinetics cohort and in the two participants in the lenacapavir group who acquired HIV infection. The gray circles indicate the lenacapavir plasma concentrations in individual participants in the pharmacokinetics cohort. The solid gray line indicates the median lenacapavir concentration in the pharmacokinetics cohort. The dashed gray lines indicate the 5th and 95th percentiles in the pharmacokinetics cohort. The inhibitory quotient (IQ) was defined as the protein-adjusted 95% effective concentration in MT-4 cells, and IQ4 as four times the protein-adjusted 95% effective concentration in vitro.[31] IQ1 was 3.9 ng per milliliter, and IQ4 was 15.5 ng per milliliter. The lenacapavir plasma concentrations for Participant A at weeks 4, 8, and 13 were 26 ng per milliliter (IQ6.7), 25.4 ng per milliliter (IQ6.6), and 23.8 ng per milliliter (IQ6.2), respectively. Participant A received the diagnosis at week 13, with positive rapid and central-laboratory fourth-generation antigen–antibody tests, an antibody differentiation test that was indeterminate for HIV-1 and negative for HIV-2, a positive qualitative RNA test, and an HIV-1 viral load of 934,000 copies per milliliter. Retrospective viral-load testing from week 8 was negative according to standard HIV testing (lower limit of quantification, 20 copies per milliliter), and HIV-1 RNA single-copy testing showed a result of 4.8 copies per milliliter. All other samples were negative according to HIV-1 RNA single-copy assay. The lenacapavir plasma concentrations for Participant B at weeks 4, 8, 13, and 26 were 10.6 ng per milliliter (IQ2.7), 5.1 ng per milliliter (IQ1.3), 15.1 ng per milliliter (IQ3.9), and 25.2 ng per milliliter (IQ6.5), respectively. Participant B received the diagnosis at week 26, with a negative rapid fourth-generation antigen–antibody test, positive central-laboratory fourth-generation antigen–antibody test, an antibody differentiation test that was indeterminate for HIV-1 and negative for HIV-2, a positive qualitative RNA test, and an HIV-1 viral load of 14,100 copies per milliliter. Retrospective standard viral-load testing from week 13 was negative (lower limit of quantification, 20 copies per milliliter), as was HIV-1 RNA single-copy assay. Injection-visit adherence after the clinical hold in the lenacapavir group was 90.4% at week 26 and 93.3% at week 52. Panel B shows adherence in the F/TDF group. Low adherence was defined as a tenofovir diphosphate concentration of less than 350 fmol per dried-blood-spot punch, medium adherence as 350 to less than 700 fmol per punch, and high adherence as 700 fmol or more per punch. Tenofovir diphosphate concentrations in dried-blood-spot samples reflect the average adherence over the preceding 8 to 12 weeks.[33] Of nine seroconversions in the F/TDF group, eight participants had available dried-blood-spot samples for analysis. Diagnoses of HIV infection in the F/TDF group occurred at week 8 (in one participant who had a result from dried-blood-spot testing below the limit of quantification), week 13 (in one participant for whom a dried-blood-spot sample was not available and who had discontinued F/TDF ≥10 days before diagnosis), week 26 (in one participant who had taken <two doses per week and in one participant who had a result from dried-blood-spot testing below the limit of quantification), week 39 (in two participants with dried-blood-spot testing results below the limit of quantification and in one participant who had a result from dried-blood-spot testing below the limit of quantification and had discontinued F/TDF ≥10 days before diagnosis), week 52 (in one participant who had taken <two doses per week and had discontinued F/TDF ≥10 days before diagnosis), and week 65 (in one participant who had a result from dried-blood-spot testing below the limit of quantification).

(11.3%) in the lenacapavir group and in 147 of 1071 participants (13.7%) in the F/TDF group (Table S15).

INJECTION-SITE REACTIONS

A total of 10,094 lenacapavir injections were administered in the lenacapavir group, and 5145 placebo injections were administered in the F/TDF group. Injection-site reactions were reported in 1816 participants (83.2%) in the lenacapavir group and in 756 (69.5%) in the F/TDF group. Most injection-site reactions were mild (grade 1) or moderate (grade 2) in severity (Fig. S4). Subcutaneous nodules, pain, and erythema were the most commonly reported injection-site reactions in both the lenacapavir group and the F/TDF group. Subcutaneous nodules occurred more frequently in the lenacapavir group than in the F/TDF group (63.4% vs. 39.2%). Among the participants in the lenacapavir group, the median duration of injection-site nodules was 183 days (interquartile range, 89 to 274), and the median duration of induration was 84 days (interquartile range, 8 to 190). Among the participants in the F/TDF group, the median duration of injection-site nodules was 64 days (interquartile range, 19 to 98), and the median duration of induration was 8 days (interquartile range, 5 to 57). The median diameter of the largest nodule per participant was 3.0 cm (interquartile range, 2.0 to 4.0) in the lenacapavir group and 2.0 cm (interquartile range, 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%). Keloid formation in response to injection was not reported. The frequency and sever-

Table 2. Safety Findings.*

Variable	Lenacapavir (N=2183)	F/TDF (N=1088)
	number (percent)	
Adverse event†		
Any grade	1607 (73.6)	803 (73.8)
Grade ≥2	1173 (53.7)	594 (54.6)
Grade ≥3	91 (4.2)	65 (6.0)
Serious adverse event	71 (3.3)	43 (4.0)
Adverse event leading to discontinuation of trial regimen‡	7 (0.3)	7 (0.6)
Death§	4 (0.2)	2 (0.2)
Adverse events occurring in ≥3% of the participants†		
Rectal chlamydia infection	289 (13.2)	128 (11.8)
Oropharyngeal gonococcal infection	283 (13.0)	119 (10.9)
Rectal gonococcal infection	233 (10.7)	99 (9.1)
Upper respiratory tract infection	148 (6.8)	77 (7.1)
Diarrhea	146 (6.7)	75 (6.9)
Headache	119 (5.5)	76 (7.0)
Influenza	120 (5.5)	66 (6.1)
Latent syphilis	114 (5.2)	44 (4.0)
Nausea	89 (4.1)	67 (6.2)
Covid-19	69 (3.2)	44 (4.0)
Nasopharyngitis	69 (3.2)	39 (3.6)
Syphilis	71 (3.3)	34 (3.1)
Gastroenteritis	66 (3.0)	31 (2.8)
Pharyngeal chlamydia infection	55 (2.5)	40 (3.7)
Injection-site reactions¶		
Serious injection-site reaction	0	0
Injection-site reaction leading to premature discontinuation of the trial regimen	26 (1.2)	3 (0.3)
Severity		
Any grade	1816 (83.2)	756 (69.5)
Grade 1	1441 (66.0)	594 (54.6)
Grade 2	361 (16.5)	161 (14.8)
Grade 3‖	14 (0.6)	1 (<0.1)
Grade 4	0	0
Laboratory abnormalities**		
Any grade	1822/2153 (84.6)	937/1071 (87.5)
Grade 1	577/2153 (26.8)	232/1071 (21.7)
Grade 2	1002/2153 (46.5)	558/1071 (52.1)
Grade 3	184/2153 (8.5)	122/1071 (11.4)
Grade 4	59/2153 (2.7)	25/1071 (2.3)

* Covid-19 denotes coronavirus disease 2019.
† Data on injection-site reactions are not included in this category.
‡ The only adverse event that led to discontinuation of the trial regimen that occurred in more than 1 participant in either group was a decrease in creatinine clearance (in 2 participants [0.2%] in the F/TDF group).
§ The deaths in the lenacapavir group were due to cerebrovascular accident and pulmonary thromboembolism, car collision, sudden death with an undetermined cause, and suicide. The deaths in the F/TDF group were due to intracranial hemorrhage and undetermined cause. None were considered by the investigator to be related to the trial regimen.
¶ Injection-site reaction events were categorized according to the *Medical Dictionary for Regulatory Activities*, version 27.0, high-level term. A total of 2183 participants in the lenacapavir group and 1088 participants in the F/TDF group received at least one injection.
‖ Grade 3 injection-site reactions included ulcers in 7 participants (0.3%) in the lenacapavir group (additional details are provided in Table S13).
** The denominators are based on participants with postbaseline values.

ity of injection-site reactions diminished with subsequent injections. 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.

DISCUSSION

Twice-yearly subcutaneous lenacapavir was efficacious for prevention of HIV infection in a population of cisgender gay, bisexual, and other men, transgender women, transgender men, and gender-nonbinary persons, and no safety concerns were identified. In addition, lenacapavir was more efficacious than daily oral F/TDF in preventing HIV infection. The efficacy and the safety profile of lenacapavir were consistent with previous results in cisgender women.[14] It is notable that lenacapavir showed superior efficacy to F/TDF, even in the context of relatively high adherence to daily oral PrEP, although oral adherence did decline over time, and the breakthrough infections were associated with low adherence to F/TDF.

There is growing recognition among clinical researchers, regulatory agencies, and other stakeholders that increasing inclusion and diversity in clinical trials is critical to ensure the generalizability of results and is a step toward equitable access to scientific innovations.[14,37,38] We used several approaches to address disparities in clinical trial participation, including the establishment of a trial-specific community advisory group, establishment of trialwide diversity goals, and selection of sites with expertise in gender-affirming care, community engagement, and location in regions most affected by the HIV epidemic (Table S16).[20,39]

The new counterfactual design, which used recency assays and the recent infection testing algorithm to estimate the incidence of HIV infection in the screening cohort, avoids the ethical issues associated with a placebo group, given that effective options exist. The design has potential limitations. For example, the population screened had certain characteristics such as no HIV testing or PrEP use for at least 3 months; however, these aspects would be consistent with a placebo group of persons with unknown HIV status who were not taking PrEP. It is reassuring to note that sexual behavioral and other characteristics of the screened population and the randomized cohort were similar. Another concern is that the approach may yield an underestimate of prospectively observed incidence of HIV infection,[40,41] and our estimated background incidence may thus be conservative.

Two participants who received lenacapavir acquired HIV infection before their second injection. It is notable that there was no evidence of delay of HIV seroconversion or delayed diagnosis with standard HIV-1 testing; these findings are in contrast to the findings from cabotegravir studies, which showed delayed diagnosis with standard HIV-1 testing.[42]

Lenacapavir is only approved for use in persons with multidrug-resistant HIV who are highly treatment-experienced, which is a limited population. There is no evidence of circulating N74D in any population, and the N74 amino acid is highly conserved in all subtypes evaluated.[43-45] Early emergence of the N74D mutation has been reported in vitro and in persons receiving lenacapavir for HIV treatment, which suggests, along with the HIV testing described, that the two cases of HIV infection in the lenacapavir group in this trial were infections that occurred during the trial period, with emergence of capsid resistance resulting from lenacapavir monotherapy.[10,46] As in the companion trial (PURPOSE 1),[14] all the participants were offered open-label lenacapavir and will continue to be monitored closely for new HIV infections, including for potential delays in HIV diagnosis or development of resistance. Similar emergence of resistance in HIV infections acquired during the use of PrEP have been reported.[47,48] Cases of HIV infection despite use of F/TDF PrEP have been reported, often in the context of high exposures to HIV and repeated mucosal injury.[49] It is noteworthy, however, that more than 99% of the participants in the lenacapavir group did not acquire HIV infection, despite the high levels of sexual exposure, use of drugs in conjunction with sex ("chemsex"), and sexually transmitted infections.

There were no differences in the incidence of the most common adverse events or laboratory abnormalities between the lenacapavir and F/TDF groups, with the exception of a decline from baseline in median estimated glomerular filtration rate in the F/TDF group, a result consistent with expected changes with the use of F/TDF.[50] Injection-site reactions were common with both lenacapavir and placebo injections. The most frequently observed injection-site reactions to lenacapavir were nodules and pain, with the incidence and severity decreasing over time, which has been

observed in previous trials of injectable PrEP and in PrEP and HIV treatment trials with lenacapavir.[11,14,51,52] Both nodules and pain are consistent with the mechanism of action and delivery of subcutaneous injectable lenacapavir. The injection-site nodules generally represent a nonvisible but sometimes palpable subcutaneous drug depot that resolves or decreases in size as the drug elutes out over time; some people in HIV treatment trials who had biopsies of nodules had evidence of a foreign body or a granulomatous response.[13,35,53,54] The incidence of injection-site pain among participants in the lenacapavir group was similar to that among participants in the F/TDF group, who received placebo injections, suggesting that the pain was due to an injection, rather than the agent. A few participants had injection-site ulcers that were most likely due to inadvertent intradermal injections from inappropriately administered subcutaneous injections that were too shallow.

There are several potential explanations for the decrease in nodules, pain, and erythema over subsequent injections. As clinical experience with lenacapavir injections increased, the preinjection counseling to participants on what to expect improved. In addition, improved injection technique and pain mitigation efforts, including administration of ice or a cold compress before and after the injection, were implemented during the trial.[35] Finally, participants may have become more accustomed to the injection experience and reported fewer concerns with subsequent injections.

Twice-yearly lenacapavir offers an efficacious choice for prevention of HIV infection, which may increase PrEP uptake.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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