ORIGINAL ARTICLE

Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women

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ABSTRACT

BACKGROUND

There are gaps in uptake of, adherence to, and persistence in the use of preexposure prophylaxis for human immunodeficiency virus (HIV) prevention among cisgender women.

METHODS

We conducted a phase 3, double-blind, randomized, controlled trial involving adolescent girls and young women in South Africa and Uganda. Participants were assigned in a 2:2:1 ratio to receive subcutaneous lenacapavir every 26 weeks, daily oral emtricitabine–tenofovir alafenamide (F/TAF), or daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF; active control); all participants also received the alternate subcutaneous or oral placebo. We assessed the efficacy of lenacapavir and F/TAF by comparing the incidence of HIV infection with the estimated background incidence in the screened population and evaluated relative efficacy as compared with F/TDF.

RESULTS

Among 5338 participants who were initially HIV-negative, 55 incident HIV infections were observed: 0 infections among 2134 participants in the lenacapavir group (0 per 100 person-years; 95% confidence interval [CI], 0.00 to 0.19), 39 infections among 2136 participants in the F/TAF group (2.02 per 100 person-years; 95% CI, 1.44 to 2.76), and 16 infections among 1068 participants in the F/TDF group (1.69 per 100 person-years; 95% CI, 0.96 to 2.74). Background HIV incidence in the screened population (8094 participants) was 2.41 per 100 person-years (95% CI, 1.82 to 3.19). HIV incidence with lenacapavir was significantly lower than background HIV incidence (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.04; P<0.001) and than HIV incidence with F/TDF (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.10; P<0.001). HIV incidence with F/TAF did not differ significantly from background HIV incidence (incidence rate ratio, 0.84; 95% CI, 0.55 to 1.28; P=0.21), and no evidence of a meaningful difference in HIV incidence was observed between F/TAF and F/TDF (incidence rate ratio, 1.20; 95% CI, 0.67 to 2.14). Adherence to F/TAF and F/TDF was low. No safety concerns were found. Injection-site reactions were more common in the lenacapavir group (68.8%) than in the placebo injection group (F/TAF and F/TDF combined) (34.9%); 4 participants in the lenacapavir group (0.2%) discontinued the trial regimen owing to injection-site reactions.

CONCLUSIONS

No participants receiving twice-yearly lenacapavir acquired HIV infection. HIV incidence with lenacapavir was significantly lower than background HIV incidence and HIV incidence with F/TDF. (Funded by Gilead Sciences; PURPOSE 1 ClinicalTrials.gov number, NCT04994509.)

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Cisgender women account for approximately half the 1.3 million new human immunodeficiency virus (HIV) infections that occur worldwide each year.[1] The first HIV preexposure prophylaxis (PrEP) medication, daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF), is effective if taken as directed,[2,3] and more than 6 million persons are estimated to have started PrEP since the first approval of F/TDF by the Food and Drug Administration (FDA) in 2012.[4] However, women's uptake of, adherence to, and persistence in the use of PrEP remains limited worldwide, which underscores the need to develop new options.[1,5-9]

Lenacapavir is a novel, first-in-class, multistage HIV-1 capsid inhibitor with high potency and a long half-life, allowing administration by subcutaneous injection twice yearly.[10,11] Tenofovir alafenamide (TAF) is an orally bioavailable HIV reverse transcriptase inhibitor with increased plasma stability and more rapid uptake by peripheral-blood mononuclear cells than TDF.[12] Coformulated with emtricitabine, F/TAF is administered in a smaller tablet than F/TDF and is similarly effective for PrEP in cisgender men and transgender women who have sex with men.[13] Both lenacapavir[11] and F/TAF,[14] in combination with other antiretroviral agents, are used for HIV treatment. In nonhuman primate models, capsid inhibitors and tenofovir-based agents have high preclinical efficacy against simian HIV acquisition in vaginal challenge models of PrEP.[15-17] We evaluated the safety and efficacy of twice-yearly subcutaneous lenacapavir or daily oral F/TAF for HIV prevention in adolescent girls and young women.

METHODS

TRIAL DESIGN

We conducted a phase 3, multicenter, double-blind, randomized, active-controlled trial (PURPOSE 1). The primary objective was to determine the efficacy of lenacapavir or F/TAF, in parallel, for HIV prevention, by comparing the prospectively measured HIV incidence for each investigational agent with the background HIV incidence among screened persons (the cross-sectional incidence cohort) (Fig. 1A). We also assessed the relative efficacy of each drug as compared with HIV incidence in an active internal control group receiving daily oral F/TDF (the randomized cohort). This new background-HIV-incidence design was based on a consensus statement for how to conduct next-generation HIV prevention trials that was generated by academic researchers, regulators, pharmaceutical innovators, and other stakeholders.[18] Alternative randomized designs had substantial limitations: noninferiority to F/TDF was infeasible and violated the constancy assumption (given the inconsistent efficacy of F/TDF in previous trials involving women and variable adherence and effectiveness of F/TDF since the initial placebo-controlled trials),[19,20] and superiority to placebo was unethical (given the international guidelines recommending F/TDF PrEP across populations). The chosen design could directly assess the efficacy of both lenacapavir and F/TAF. We developed the protocol in collaboration with the principal investigators and the PURPOSE 1 Global Community Advisory and Accountability Group of PrEP community advocates.[21] The trial protocol is available with the full text of this article at NEJM.org, and detailed methods are provided in the Supplementary Appendix, also available at NEJM.org.

PARTICIPANTS AND PROCEDURES

We selected trial locations in South Africa (25) and Uganda (3) where the HIV incidence among adolescent girls and young women not receiving PrEP was at least 3.5 per 100 person-years in recent trials.[22,23] Adolescent girls and young women (16 to 25 years of age) who were sexually active with male partners, were not using PrEP, and had unknown HIV status and no HIV testing within the previous 3 months (to avoid biasing the cross-sectional incidence cohort toward persons less likely than the local population to have HIV infection) were eligible.

In the cross-sectional incidence cohort, participants underwent HIV testing with an FDA-approved, rapid, point-of-care fourth-generation antibody–antigen test, a central laboratory fourth-generation antigen–antibody test that, if positive, was reflexively confirmed by an antibody assay to differentiate between HIV types 1 and 2 (HIV-1 and HIV-2, respectively), 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 (lower limit of quantification, 20 copies per milliliter). We further

tested HIV-positive samples for recent HIV infection with the limiting antigen antibody avidity assay (LAg-EIA, Sedia Biosciences) (Fig. S5).[24] All participants and personnel were not aware of the results of the LAg-EIA assay for recent infection or the estimated background HIV incidence.

Participants who received a diagnosis of HIV infection were referred for local HIV care, and we randomly assigned HIV-negative participants in a 2:2:1 ratio to receive subcutaneous lenacapavir (927 mg, in two 1.5-ml injections) every 26 weeks (within a window of ±7 days), daily oral F/TAF (200 mg of emtricitabine and 25 mg of TAF), or daily oral F/TDF (200 mg of emtricitabine and 300 mg of TDF). Participants in the lenacapavir group received placebo tablets matching either F/TAF or F/TDF (in a 2:1 ratio); participants in the F/TAF and F/TDF groups received placebo injections matching lenacapavir. Participants receiving lenacapavir received loading doses of two 300-mg tablets of lenacapavir on each of days 1 and 2; participants receiving F/TAF or F/TDF received two tablets of matched lenacapavir placebo on each of days 1 and 2.

Randomization was centralized, not stratified, and had a block size of 10. All the participants and personnel involved in the conduct of the trial were unaware of the trial-group assignments except for the personnel who prepared or administered the injection.

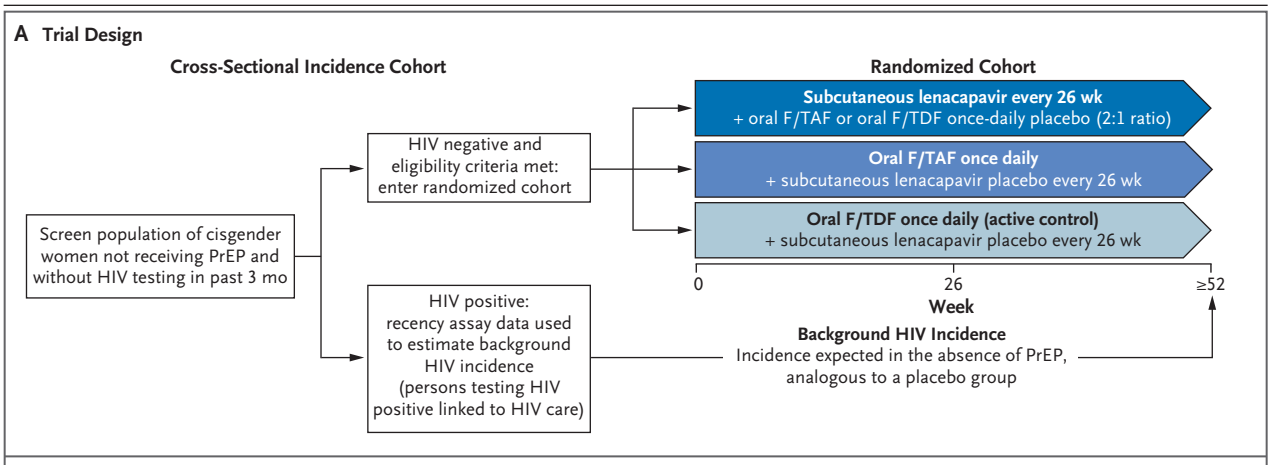
Randomly assigned participants were seen for follow-up at weeks 4, 8, and 13 and every 13 weeks thereafter. At each visit, we conducted safety laboratory, pregnancy, and HIV testing (with both rapid point-of-care and central laboratory fourth-generation antigen–antibody testing, which if positive was confirmed with reflexive HIV-1 and HIV-2 differentiation antibody assay testing and qualitative HIV-1 RNA testing if antibody–antigen and antibody differentiation results were discrepant), and we archived blood samples. At baseline and every 26 weeks thereafter, all the participants received screening for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* infection and syphilis.

At each follow-up visit, individualized trial-drug adherence counseling according to local PrEP guidelines was conducted and visit attendance counseling was provided. Participants also received standard-care HIV prevention counseling (including provision of male and female condoms and lubricant), reproductive health counseling (contraception was not required but was provided if pregnancy was not desired), and evaluation of intimate partner violence or social harm from trial participation with appropriate referrals for support and counseling. Participants who became pregnant could choose to remain in the trial and continue the trial drug after a new informed-consent process reviewing the benefits and risks. Treatment of sexually transmitted infections was provided according to local guidelines. Participants with incident HIV infection received counseling and referral to local HIV care, including antiretroviral therapy initiation and follow-up through virologic suppression.

Adherence to lenacapavir therapy was defined as on-time injection (within 28 weeks after the last injection). Participants who presented later than 28 weeks after their previous injection underwent quantitative HIV-1 RNA testing in addition to rapid point-of-care antibody–antigen and central laboratory antibody–antigen testing. Participants who resumed the injection regimen later 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 to oral F/TAF and F/TDF therapy was assessed on the basis of tenofovir diphosphate levels in red cells in dried-blood-spot samples from all trial visits from a randomly preselected 10% of participants in each group. Adherence levels were defined as low (<2 tablets per week), medium (2 or 3 tablets per week), or high (≥4 tablets per week), on the basis of tenofovir diphosphate concentration thresholds previously established for TAF and TDF.[25,26] To assess the association between adherence and efficacy, a matched case–control analysis was conducted among participants in the F/TAF group who acquired HIV infection and five controls; tenofovir diphosphate levels in dried-blood-spot samples were measured from the HIV diagnosis visit or a time-matched visit for controls. Participants who chose to discontinue the blinded trial product were offered open-label F/TDF.

PRIMARY END POINTS

The primary efficacy end point was incident HIV infection among randomly assigned participants. Positive HIV testing results were reviewed by a three-member adjudication panel whose members were unaware of the trial-group assignments to confirm the closest visit date after HIV acquisi-



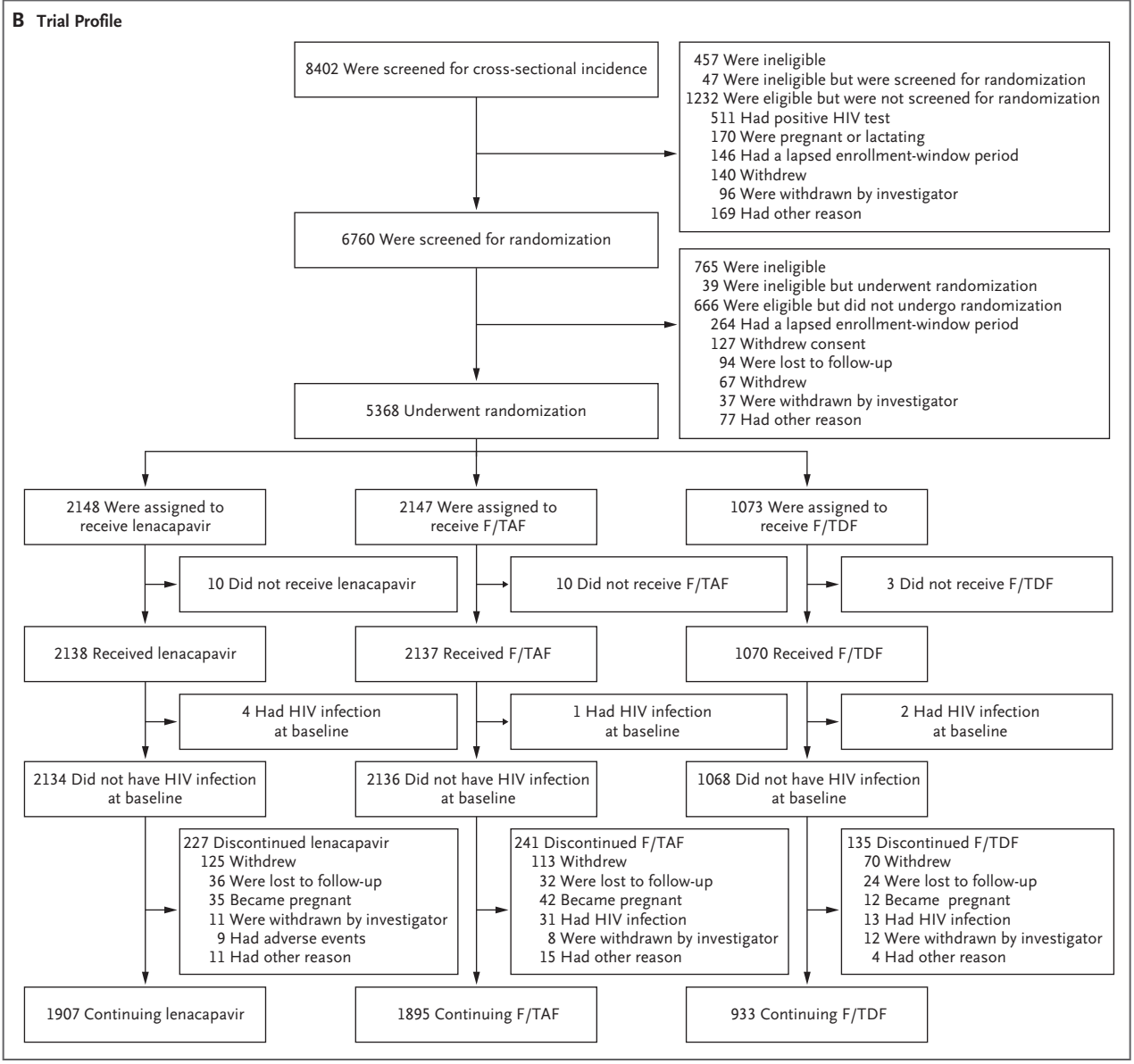


Figure 1 (facing page). Trial Design and Trial Profile.
Panel A shows the trial design. The trial began with a specialized screening process that allowed for the cross-sectional estimation of the background human immunodeficiency virus (HIV) incidence among adolescent girls and young women who were screened for the trial. Eligible participants (who had an age of 16 to 25 years, no HIV testing in the preceding 3 months, and no use of preexposure prophylaxis [PrEP] in the preceding 3 months and who were sexually active, defined as having had ≥2 vaginal intercourse encounters within the past 3 months with male partners) underwent rapid and central laboratory HIV testing, and those found to have HIV infection underwent additional testing with an assay assessing the recency of HIV infection. Participants with HIV infection were referred for care, and their participation in the trial ended. Of the 8402 participants who were screened for the cross-sectional incidence estimation, 8094 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 HIV incidence, which was derived from their HIV test and recency assay results with the use of a recent infection testing algorithm. Background HIV incidence was a cross-sectional estimate derived during the screening period; there was no longitudinal follow-up for the background incidence estimate. Participants who participated in the cross-sectional incidence estimation 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, having an estimated glomerular filtration rate of ≥60 ml per minute, and not being pregnant). These participants were randomly assigned in a 2:2:1 ratio to receive lenacapavir, emtricitabine–tenofovir alafenamide (F/TAF), or emtricitabine–tenofovir disoproxil fumarate (F/TDF) along with corresponding injection or oral tablet placebo. The first participant was screened in August 2021, the 50th percentile participant underwent randomization in May 2023, and the last participant underwent randomization in September 2023. Panel B shows the trial profile. Trial screening was conducted in two stages. Participants first underwent screening for participation in the cross-sectional incidence estimation (8402 were screened). Participants who were eligible and participated in the cross-sectional background HIV estimation could then be screened for randomization (6760 participants). Those who were eligible and desired to continue in the trial proceeded to randomization (5368 participants). After randomization, 23 participants never received a trial drug or placebo, and 7 participants were found to have HIV infection on the basis of testing performed at the baseline visit (Table S6). Overall retention and the proportion of participants continuing the blinded trial regimen at the time of analysis were similar across the trial groups (Table S8); the reasons for premature discontinuation were similar, with the exception of discontinuations due to HIV acquisition, which occurred only in the F/TAF and F/TDF groups.

tion. Efficacy analyses used a modified intention-to-treat approach that excluded participants who were adjudicated 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.

TRIAL OVERSIGHT

The trial was approved by South African, Ugandan, and U.S. regulatory authorities and the institutional review board or ethics committee at each site and was conducted in compliance with Good Clinical Practice and Good Participatory Practice Guidelines.[27] All participants or guardians provided written informed consent; adolescents 16 or 17 years of age provided assent with guardian consent unless local ethics guidelines allowed them to consent for themselves. Gilead Sciences designed the trial with input from trial investigators and the Global Community Advisory and Accountability Group; the trial investigators and staff gathered the data; and Gilead Sciences monitored the conduct of the trial, received the data, and performed the statistical analyses. All the authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The second author wrote the first draft of the manuscript in close collaboration with the first author and last two authors. All the authors reviewed the manuscript, provided feedback, and made the decision to submit the manuscript for publication.

On June 18, 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 efficacy and safety analysis for the trial. Participants began to be made aware of the trial-group assignments and were offered the option to receive lenacapavir in an open-label fashion beginning on July 8, 2024.

STATISTICAL ANALYSIS

We calculated the background HIV incidence in the cross-sectional incidence cohort using a recent infection testing algorithm.[28,29] The primary efficacy analysis was the incidence rate ratio comparing the HIV incidence among participants

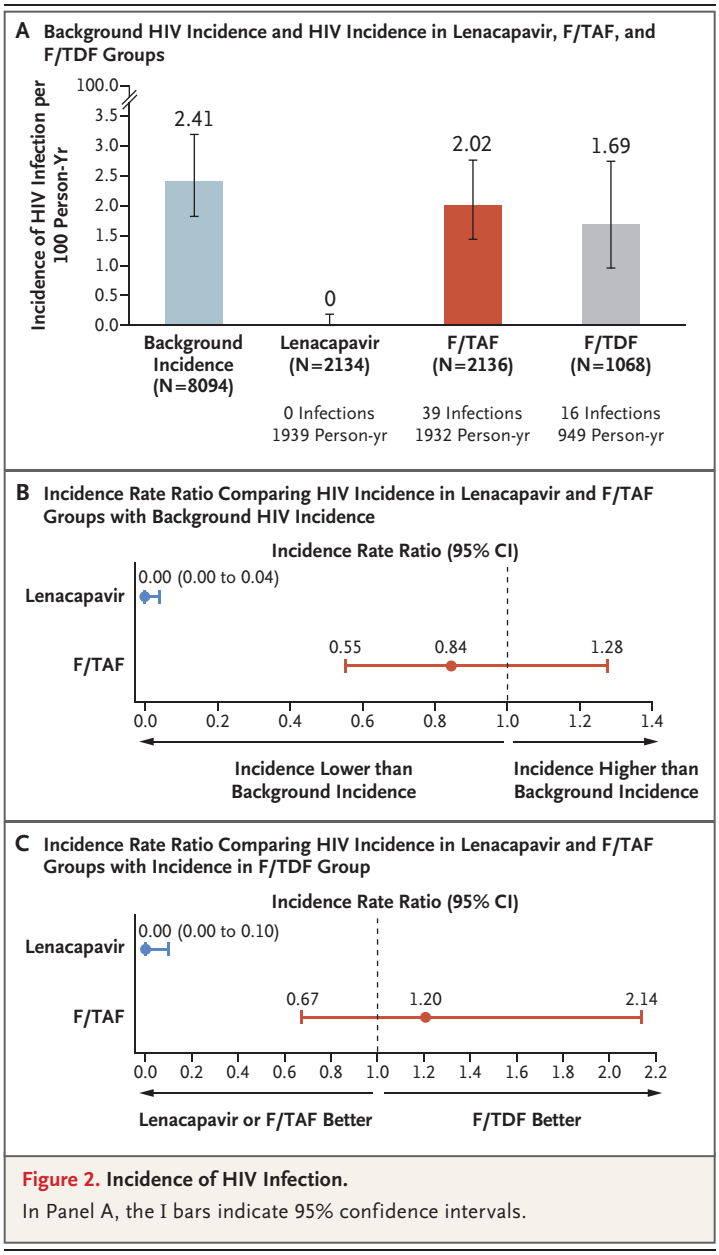


Figure 2. Incidence of HIV Infection.

In Panel A, the I bars indicate 95% confidence intervals.

assigned to receive lenacapavir or F/TAF with the background HIV incidence; this ratio was determined with the use of a Wald test or, if there were no infections, a likelihood ratio test.[29,30] The secondary efficacy analysis was the incidence rate ratio comparing the HIV incidence among participants assigned to receive lenacapavir or F/TAF with the HIV incidence among those assigned to receive F/TDF; this ratio was determined with the use of Poisson regression or, if there were no infections, an exact conditional Poisson regression model. We estimated that a sample of 5010 participants (randomly assigned in a 2:2:1 ratio to the lenacapavir, F/TAF, and F/TDF groups) would provide the trial with more than 95% power to show a 20% lower HIV incidence in the lenacapavir and F/TAF groups separately than the background HIV incidence, assuming a background HIV incidence of at least 3 per 100 person-years.

The F/TAF adherence–efficacy association was assessed by means of exact conditional logistic regression. Characteristics of the cross-sectional incidence cohort and randomized cohort were summarized descriptively, along with adverse events (including injection-site reactions and laboratory abnormalities) that were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1; adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 27.0. At a planned interim analysis occurring when 50% of the randomly assigned participants had completed at least 52 weeks of follow-up (cutoff dates, May 28, 2024, for clinical data and May 29, 2024, for laboratory data), we tested the prespecified efficacy hypotheses using a gated fixed-sequence approach with a one-sided alpha level of 0.0026 to control type I error (Fig. S3). Analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PARTICIPANT CHARACTERISTICS AND BACKGROUND HIV INCIDENCE

From August 30, 2021, to August 31, 2023, we screened 8402 adolescent girls and young women; 504 of 8094 who had a central HIV test performed (6.2%) received a diagnosis of HIV infection, of whom 92 (18.3%) were classified as recently infected (Fig. 1B). The background HIV incidence in the screened population was 2.41 per 100 person-years (95% confidence interval [CI], 1.82 to 3.19) (Fig. 2A).

A total of 5345 participants underwent randomization and received at least one dose of a trial drug or placebo. Of these, 7 were subsequently determined to have had HIV infection at the time of randomization (Table S6), and thus 5338 were included in the modified intention-to-treat efficacy analysis: 2134 in the lenacapavir group, 2136 in the F/TAF group, and 1068 in the

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

Characteristic	Lenacapavir (N=2138)	F/TAF (N=2137)	F/TDF (N=1070)
Age			
Median (range) — yr	21 (16–25)	21 (16–26)†	21 (16–25)
16 or 17 yr — no. (%)	56 (2.6)	45 (2.1)	23 (2.1)
Black race — no. (%)‡	2135 (99.9)	2136 (>99.9)	1068 (99.8)
Education — no./total no. (%)			
No primary school	17/2136 (0.8)	19/2134 (0.9)	3/1069 (0.3)
Primary school	235/2136 (11.0)	223/2134 (10.4)	106/1069 (9.9)
Secondary school	1701/2136 (79.6)	1694/2134 (79.4)	851/1069 (79.6)
College or university	183/2136 (8.6)	198/2134 (9.3)	109/1069 (10.2)
Married — no./total no. (%)	26/2136 (1.2)	30/2134 (1.4)	17/1069 (1.6)
Living with primary partner — no./total no. (%)	148/2136 (6.9)	132/2134 (6.2)	73/1069 (6.8)
Sexually transmitted infection			
Chlamydia trachomatis	520 (24.3)	562 (26.3)	263 (24.6)
Neisseria gonorrhoeae	197 (9.2)	178 (8.3)	90 (8.4)
Trichomonas vaginalis	154 (7.2)	165 (7.7)	82 (7.7)
Syphilis	57 (2.7)	63 (2.9)	29 (2.7)
Any previous use of PrEP — no. (%)	143 (6.7)	121 (5.7)	71 (6.6)
Any previous HIV testing — no. (%)	1713 (80.1)	1731 (81.0)	860 (80.4)
Median time since last HIV test (IQR) — mo	6.8 (4.7–11.5)	6.6 (4.8–11.0)	6.5 (4.6–11.0)
Country — no. (%)			
South Africa	1809 (84.6)	1790 (83.8)	909 (85.0)
Uganda	329 (15.4)	347 (16.2)	161 (15.0)

* F/TAF denotes emtricitabine–tenofovir alafenamide, F/TDF emtricitabine–tenofovir disoproxil fumarate, HIV human immunodeficiency virus, IQR interquartile range, and PrEP preexposure prophylaxis.
† One person was screened at 25 years of age but was 26 years of age by the time of randomization. This was not a violation of the eligibility criteria.
‡ Race was reported by the participants. All non-Black participants were multiracial.

F/TDF group. The baseline characteristics of the participants were similar in the three groups (Table 1). The median age of the participants was 21 years (range, 16 to 26), and 124 participants (2.3%) were younger than 18 years of age. Most participants (4304 [80.5%]) had undergone previous HIV testing; a minority (335 [6.3%]) reported any previous use of PrEP. Baseline laboratory-based diagnoses of sexually transmitted infections were common, with *C. trachomatis* infection in 1345 participants (25.2%), *N. gonorrhoeae* infection in 465 (8.7%), *T. vaginalis* infection in 401 (7.5%), and syphilis in 149 (2.8%). Baseline demographic and clinical characteristics were similar in the cross-sectional incidence cohort, in the randomized cohort, and among the participants who did not undergo randomization (Table S7).

FOLLOW-UP AND ADHERENCE

Overall, all the participants completed at least one postrandomization visit for HIV testing, and 4821 person-years of follow-up were accrued for the assessment of incident HIV infection. Overall retention was 96.7% (4855 of 5020 participants) at week 26, 93.4% (2439 of 2612 participants) at week 52, and 91% (39 of 43 participants) at week 104 (Table S8). Retention was similar across trial groups: in the lenacapavir group, 96.7% (1940 of 2007 participants) at week 26, 93.7% (985 of 1051 participants) at week 52, and 95% (18 of 19 participants) at week 104; in

the F/TAF group, 96.9% (1952 of 2014 participants), 93.5% (973 of 1041 participants), and 94% (15 of 16 participants), respectively; and in the F/TDF group, 96.4% (963 of 999 participants), 92.5% (481 of 520 participants), and 75% (6 of 8 participants), respectively (Fig. 1B). Injections were administered on time for 91.5% of the participants (4545 of 4967) at week 26 and for 92.8% of the participants (2025 of 2181) at week 52; the percentages were similar across the lenacapavir, F/TAF, and F/TDF groups. Among the preselected 10% sample of participants assessed for tenofovir diphosphate levels, most participants in both the F/TAF and F/TDF groups had low adherence; adherence decreased over time (Fig. 3A).

EFFICACY

A total of 55 incident HIV infections were observed: 0 in the lenacapavir group (0 per 100 person-years; 95% CI, 0.00 to 0.19), 39 in the F/TAF group (2.02 per 100 person-years; 95% CI, 1.44 to 2.76), and 16 in the F/TDF group (1.69 per 100 person-years; 95% CI, 0.96 to 2.74) (Fig. 2A). Lenacapavir reduced HIV incidence by 100% as compared with background HIV incidence (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.04; P<0.001) (Fig. 2B) and by 100% as compared with F/TDF (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.10; P<0.001) (Fig. 2C).

HIV incidence with F/TAF did not differ significantly from background HIV incidence (incidence rate ratio, 0.84; 95% CI, 0.55 to 1.28; P=0.21) (Fig. 2B), and there was no evidence of a meaningful difference in HIV incidence between F/TAF and F/TDF (incidence rate ratio, 1.20; 95% CI, 0.67 to 2.14) (Fig. 2C). Most participants with incident HIV infection had low or no detection of tenofovir diphosphate (34 of 37 participants in the F/TAF group and 13 of 14 in the F/TDF group; 2 participants in each group had missing data). In the F/TAF group, participants with medium or high adherence had a lower odds of acquiring HIV infection than those with low adherence (odds ratio, 0.11; 95% CI, 0.01 to 0.49) (Fig. 3B).

The incidence of laboratory-diagnosed *C. trachomatis*, *N. gonorrhoeae*, or *T. vaginalis* infection at asymptomatic screening every 26 weeks

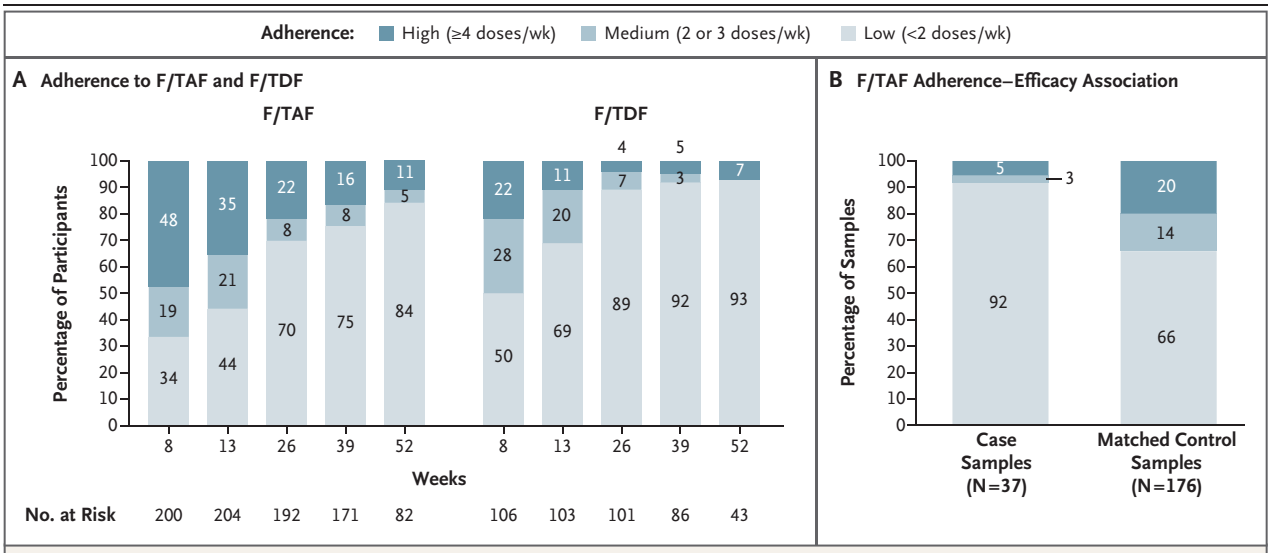


Figure 3. Adherence.

Adherence was assessed on the basis of tenofovir diphosphate levels in red cells in dried-blood-spot samples from all trial visits from a randomly preselected 10% of participants in the F/TAF and F/TDF groups (Panel A). To assess the association between adherence and HIV prevention efficacy in the F/TAF group, a matched case–control analysis was conducted (Panel B). Case participants were defined as participants who had acquired HIV infection; up to five controls were selected, matched on the basis of trial site and VOICE risk score for acquisition of HIV infection.[31] Each of 37 case participants contributed 1 sample. A trial participant could serve as a control for more than 1 case participant; 159 participants contributed 176 samples to be used as matched controls. Tenofovir diphosphate levels in dried-blood-spot samples were measured from the HIV diagnosis visit (for case participants) or time-matched visit (for controls). Percentages may not total 100 because of rounding.

was high and similar in the three groups: in the lenacapavir group, 48.7 per 100 person-years (930 events during 1908.8 person-years); in the F/TAF group, 50.8 per 100 person-years (965 events during 1899.4 person-years); and in the F/TDF group, 48.4 per 100 person-years (452 events during 933.4 person-years). More details are provided in Table S9.

SAFETY

The most common adverse events, aside from injection-site reactions, were headache (in 285 of 2138 participants [13.3%] in the lenacapavir group, in 352 of 2137 [16.5%] in the F/TAF group, and in 155 of 1070 [14.5%] in the F/TDF group), urinary tract infection (in 307 of 2138 participants [14.4%], in 305 of 2137 [14.3%], and in 163 of 1070 [15.2%], respectively), and genitourinary chlamydia infection (in 300 of 2138 participants [14.0%], in 317 of 2137 [14.8%], and in 129 of 1070 [12.1%], respectively) (Table 2). The percentage of participants with adverse events was generally similar across the trial groups, except for a lower percentage with nausea and vomiting in the lenacapavir group (6.7% and 5.8%, respectively) than in the F/TAF group (10.9% and 11.0%) and the F/TDF group (13.3% and 10.0%). The incidence of grade 3 or higher adverse events was similar across the trial groups (in 88 of 2138 participants [4.1%] in the lenacapavir group, in 95 of 2137 [4.4%] in the F/TAF group, and in 50 of 1070 [4.7%] in the F/TDF group) (Table S10), as was the incidence of serious adverse events (in 59 of 2138 participants [2.8%], in 85 of 2137 [4.0%], and in 35 of 1070 [3.3%], respectively) (Table S11) and adverse events leading to discontinuation of the trial regimen (in 5 of 2138 participants [0.2%], in 2 of 2137 [0.1%], and in none of 1070, respectively) (Table S12).

There were six deaths, all in the F/TAF group (from asphyxia resulting from strangulation, nonaccidental burns, a knife stab to the chest, hemorrhage due to a traffic accident, autopsy-confirmed ischemic cardiomyopathy, and ovarian cancer). None of the deaths were considered by the investigator to be related to a trial drug or placebo.

Laboratory abnormalities occurred in 90.5% of the participants (4792 of 5293). Most laboratory abnormalities were grade 1 or 2. In the lenacapavir group, grade 1 events occurred in 441 of 2126 participants (20.7%), and grade 2 events occurred in 1376 of 2126 (64.7%); the respective values in the F/TAF group were 430 of 2113 (20.4%) and 1371 of 2113 (64.9%) and in the F/TDF group were 197 of 1054 (18.7%) and 701 of 1054 (66.5%). Grade 3 and 4 laboratory abnormalities were less common. In the lenacapavir group, grade 3 events occurred in 92 of 2126 participants (4.3%), and grade 4 events occurred in 20 of 2126 (0.9%); the respective values in the F/TAF group were 81 of 2113 (3.8%) and 22 of 2113 (1.0%) and in the F/TDF group were 50 of 1054 (4.7%) and 11 of 1054 (1.0%) (Table S13).

There were 510 pregnancies among 487 participants: 193 pregnancies in the lenacapavir group, 219 in the F/TAF group, and 98 in the F/TDF group. At the time of the interim analysis, 277 pregnancies (54.3%) were completed, and 233 (45.7%) were ongoing. There were 121 births (23.7%), 66 spontaneous abortions (12.9%), and 90 induced abortions (17.6%) (Table S14). A congenital abnormality of polydactyly was observed in an infant born to a participant in the lenacapavir group who had a strong family history of this condition; this abnormality was considered by the investigator to be unrelated to the drug. Among pregnant participants, HIV infection occurred in no participants in the lenacapavir group, in 4 participants in the F/TAF group, and in 1 participant in the F/TDF group.

The most common adverse events were injection-site reactions. A total of 25,329 injections were administered (10,154 in 2138 participants in the lenacapavir group and 15,175 in 3206 participants receiving placebo injection in the F/TAF and F/TDF groups). Injection-site reactions reported as being related to lenacapavir or placebo or to trial procedures occurred in 1470 participants (68.8%) in the lenacapavir group and 1118 participants (34.9%) given placebo injections (Table 2), including subcutaneous nodules in 63.8% of those in the lenacapavir group and in 16.6% of those who received placebo injections. Nearly all injection-site reactions were grade 1 or 2 in severity, higher-grade reactions were rare and occurred in similar percentages of participants with lenacapavir and placebo, and no reactions were serious. The frequency of injection-site reactions diminished with subsequent injections (Fig. S6). Keloid formation was not reported. Four participants (0.2%) in the lenacapavir group discontinued the trial regimen owing to injection-site reactions, as compared with no participants who received a placebo injection.

Table 2. Safety Findings.*

Variable	Lenacapavir (N=2138)	F/TAF (N=2137)	F/TDF (N=1070)
Adverse event — no. (%)†			
Any grade	1631 (76.3)	1665 (77.9)	830 (77.6)
Grade ≥2	1111 (52.0)	1078 (50.4)	533 (49.8)
Grade ≥3	88 (4.1)	95 (4.4)	50 (4.7)
Serious adverse event — no. (%)†	59 (2.8)	85 (4.0)	35 (3.3)
Adverse event leading to discontinuation of the trial regimen — no. (%)†‡	5 (0.2)	2 (<0.1)	0
Adverse events occurring in ≥5% of participants — no. (%)†			
Headache	285 (13.3)	352 (16.5)	155 (14.5)
Urinary tract infection	307 (14.4)	305 (14.3)	163 (15.2)
Genitourinary tract chlamydia infection	300 (14.0)	317 (14.8)	129 (12.1)
Upper respiratory tract infection	271 (12.7)	274 (12.8)	121 (11.3)
Nausea	144 (6.7)	234 (10.9)	142 (13.3)
Vomiting	125 (5.8)	235 (11.0)	107 (10.0)
Vaginal discharge	166 (7.8)	191 (8.9)	87 (8.1)
Vulvovaginal candidiasis	146 (6.8)	172 (8.0)	67 (6.3)
Genitourinary tract gonococcal infection	141 (6.6)	157 (7.3)	66 (6.2)
Diarrhea	133 (6.2)	161 (7.5)	67 (6.3)
Dizziness	120 (5.6)	141 (6.6)	79 (7.4)
Death — no.§	0	6	0
Laboratory abnormalities			
No. of participants with at least one postbaseline laboratory result	2126	2113	1054
Grade — no. (%)			
Any	1929 (90.7)	1904 (90.1)	959 (91.0)
1	441 (20.7)	430 (20.4)	197 (18.7)
2	1376 (64.7)	1371 (64.9)	701 (66.5)
3	92 (4.3)	81 (3.8)	50 (4.7)
4	20 (0.9)	22 (1.0)	11 (1.0)
Injection-site reactions¶			
No. of participants who received at least one injection	2138	2136	1070
Serious injection-site reaction — no. (%)	0	0	0
Injection-site reaction leading to premature discontinuation of the trial regimen — no. (%)	4 (0.2)	0	0
Grade — no. (%)			
Any	1470 (68.8)	755 (35.3)	363 (33.9)
1	1060 (49.6)	563 (26.4)	281 (26.3)
2	406 (19.0)	190 (8.9)	80 (7.5)
3	4 (0.2)	2 (<0.1)	2 (0.2)
4	0	0	0

Table 2. (Continued.)

* Adverse events and laboratory abnormalities that are reported here were those that occurred in participants who had received at least one dose of a trial drug or placebo. Adverse events, injection-site reactions, and laboratory abnormalities were coded according to the *Medical Dictionary for Regulatory Activities*, version 27.0, and graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1.
† Data on injection-site reactions were excluded.
‡ In the lenacapavir group, one participant each had nausea, decreased creatinine clearance, increased liver-enzyme levels, spontaneous abortion, and a suicide attempt and major depression. In the F/TAF group, one participant had a combination of a suicide attempt, depressive symptoms, and a drug overdose, and one participant had angioedema.
§ No deaths were considered by the investigator to be related to a trial drug or placebo. Deaths were from asphyxia resulting from strangulation, nonaccidental burns, a knife stab to the chest, hemorrhage due to a traffic accident, autopsy-confirmed ischemic cardiomyopathy, and ovarian cancer.
¶ Injection-site reactions that are reported here were to trial-related injections only; reactions to other types of injections (e.g., vaccines) were excluded. All four injection-site reactions leading to discontinuation of the trial regimen were subcutaneous nodules (one participant discontinued owing to both a subcutaneous nodule and injection-site pain). Grade 3 injection-site reactions included six cases of injection-site ulcer (three in the lenacapavir group, two in the F/TAF group, and one in the F/TDF group), one case of nodule (in the lenacapavir group), and one case of pain (in the F/TDF group).

DISCUSSION

No adolescent girls or young women receiving twice-yearly lenacapavir acquired HIV infection in this trial. HIV incidence with lenacapavir was significantly lower than both background HIV incidence and HIV incidence with F/TDF. A twice-yearly PrEP choice could overcome challenges with respect to adherence and persistence and result in substantial protection against HIV infection for women worldwide.

We implemented several innovative trial-design features to address challenges in the evolving HIV prevention field. The new design creates a path forward for trials of future PrEP options and potentially for HIV vaccines. Previous studies indicate that the recent infection testing algorithm may yield a conservative underestimate of prospectively observed HIV incidence[32,33]; our estimated background HIV incidence was consistent with a conservative estimate but was generally in agreement with the prospectively observed incidence in the F/TDF group, with F/TDF adherence taken into account. Stakeholder engagement was key to the design of this trial and resulted in data for subpopulations that are disproportionately affected by HIV infection and that have been historically excluded from pivotal clinical trials, including pregnant and lactating women and adolescents 16 or 17 years of age. Available pregnancy outcomes were similar to those expected for the population,[34-36] and we continue to assess ongoing pregnancies and monitor outcomes, including a dedicated evaluation of lenacapavir pharmacokinetics in pregnancy and infant exposure.

Lenacapavir is injected into the subcutaneous space and forms a drug depot that may be palpable as a nodule but is usually not visible under the skin. Biopsy samples from animals and humans show that a granulomatous or foreign-body reaction to the drug depot may form.[37,38] As the drug elutes over time, the depot gets smaller, and the nodules resolve or reduce in size substantially before the next injection. Although injection-site reactions with lenacapavir were relatively common and expected, discontinuations of the drug were rare. Furthermore, the incidence of injection-site reactions, including nodules, decreased with subsequent doses, a phenomenon that has also been observed with lenacapavir in the context of HIV treatment.[38] Lenacapavir was associated with fewer gastrointestinal side effects than F/TAF and F/TDF. Breakthrough HIV infection and delayed seroconversion have been seen with other PrEP agents,[39] but we did not see evidence of a similar phenomenon for lenacapavir; further follow-up, including in the open-label extension phase of this trial, is needed.

HIV incidence in the F/TAF group did not differ significantly from background HIV incidence. Adherence to daily oral F/TAF, and to F/TDF, was poor, a finding that is consistent with previous reports of low adherence to daily oral F/TDF and therefore low effectiveness in cohorts of women, particularly younger women, across geographic areas.[6-9,40] Poor adherence to and persistence in the use of F/TAF and F/TDF may potentially be due to a variety of reasons, including stigma, dislike of or lack of experience with daily pill taking, and inaccurate perception of the likelihood of the acquisi-

tion of HIV infection. It is notable that protection against HIV infection was strongly associated with F/TAF adherence in the case–control analysis, as has been similarly seen for both F/TAF and F/TDF; these findings provide consistent evidence that daily oral PrEP works when taken.[2,3,13]

F/TDF has been approved since 2012, and the monthly dapivirine vaginal ring[41] and every-2-month intramuscular cabotegravir[39,40] have more recently provided new PrEP options. Nevertheless, PrEP use remains suboptimal among women, particularly in populations with disproportionate HIV incidence, including young women, women in Africa, women of color in the United States, and migrant women in multiple geographic areas. Twice-yearly lenacapavir offers a highly efficacious and discreet choice to potentially improve PrEP use among women.

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APPENDIX

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