Supplementary Appendix

Supplement to: Kelley CF, Acevedo-Quiñones M, Agwu AL, et al. Twice-yearly lenacapavir for HIV prevention in men and gender-diverse persons. N Engl J Med. DOI: 10.1056/NEJMoa2411858

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

Table of Contents

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Supplementary Methods

Rationale for the Study Design

A novel study design based on estimation of the counterfactual (i.e., background) HIV incidence rates was pursued to overcome the challenges of assessing efficacy of novel pre-exposure prophylaxis (PrEP) agents. Because there are effective options for PrEP approved for cisgender men and transgender women, placebo-controlled trials are not acceptable. Traditional noninferiority trials are also infeasible due to the large sample sizes and long duration of follow-up required to observe sufficient end points to achieve statistical power for comparison. Finally, superiority trials can be considered, but superiority may not be a reasonable expectation for all new PrEP agents as the F/TDF efficacy is very high, especially when participants adhere to their daily oral regimen (participant behavior). Therefore, working with a broad consortium of field experts from academia, regulatory agencies, and pharmaceutical innovators, we developed and implemented the design presented here.[1]

The study design is structured in multiple phases with structured transitions: the Incidence Phase, the Randomized Blinded Phase (RBP), the lenacapavir Open-Label Extension (OLE) Phase, and the Pharmacokinetic (PK) Tail Phase. Participants who complete each phase will be offered to transfer to the next phase (sequentially as listed).

The background HIV incidence (bHIV), computed based on the recency assay results collected from participants diagnosed with HIV-1 in the Incidence Phase using a Recent Infection Testing Algorithm (RITA), will serve as the primary comparator for evaluating the efficacy of the experimental study drug included in the RBP. Following the RBP, there are two standard design elements: the lenacapavir OLE Phase allows for further long-term efficacy and safety follow-up, and the PK Tail Phase, which is standard for long-acting HIV prevention drugs, provides known efficacious open-label oral PrEP to provide HIV prevention for participants during the time when lenacapavir concentrations may have declined to sub-protective levels following subcutaneous (SC) lenacapavir administration during the RBP or lenacapavir OLE Phase.

HIV Diagnostic Testing and Case Adjudication

HIV testing was performed at both the local site and a central laboratory. At screening and on Day 1, participants underwent a rapid, point-of-care HIV-1/2 antibody/antigen test (using Determine™, Abbott) at the trial site, along with a centralized, instrumented, fourth-generation HIV-1/2 antibody/antigen test (Siemens) and a quantitative HIV RNA nucleic acid amplification test (NAAT) using the Cobas 6800 system.

For follow-up visits, the testing protocol included the rapid fourth-generation HIV-1/2 antibody/antigen test at the local site and a repeat of the instrumented fourth-generation

antibody/antigen test at the central laboratory. If the central laboratory returned a positive result, confirmation was done using the HIV-1/2 antibody differentiation assay (Geenius^{TM} HIV 1/2 Supplemental Assay). Any conflicting or uncertain results from serological tests were further analyzed using a qualitative HIV RNA NAAT (Cobas Ampliprep-cobas TaqMan 2.0). A detailed outline of the HIV testing process is shown in Figure S1.

For participants diagnosed with a new HIV infection during the study, stored samples from prior visits were analyzed retrospectively using quantitative HIV RNA NAAT to confirm the diagnosis. An HIV Adjudication Committee, who were blinded to the treatment groups, reviewed all positive HIV test results that were obtained after the initial screening. Decisions on whether the test results indicated an actual HIV infection, a false positive, or results requiring further investigation were made by majority vote.

The panel also determined the date of diagnosis for each HIV case, defining it as the earliest study visit where evidence of infection was present. This included both prospective results from routine tests and any additional retrospective RNA testing with standard HIV RNA-1 testing. Cases were classified as incident HIV infections if they were diagnosed after Day 1 (the day of randomization), or as baseline cases if they were identified on Day 1. As anticipated, some false-positive results occurred during the trial. These cases were evaluated using additional quantitative RNA testing. A rapid HIV test was classified as a false-positive if the central laboratory's fourth-generation antibody/antigen test was negative and if a simultaneous quantitative HIV RNA test showed no detectable virus. Additionally, a positive result from the central laboratory antibody/antigen test was deemed a false positive if two consecutive quantitative HIV RNA tests, one taken at the same time and another follow-up test, both showed "none detected" results. HIV-1 RNA single-copy assay was also performed retrospectively on samples from prior to HIV-1 diagnosis (Accelevir Diagnostics, Baltimore, MD).

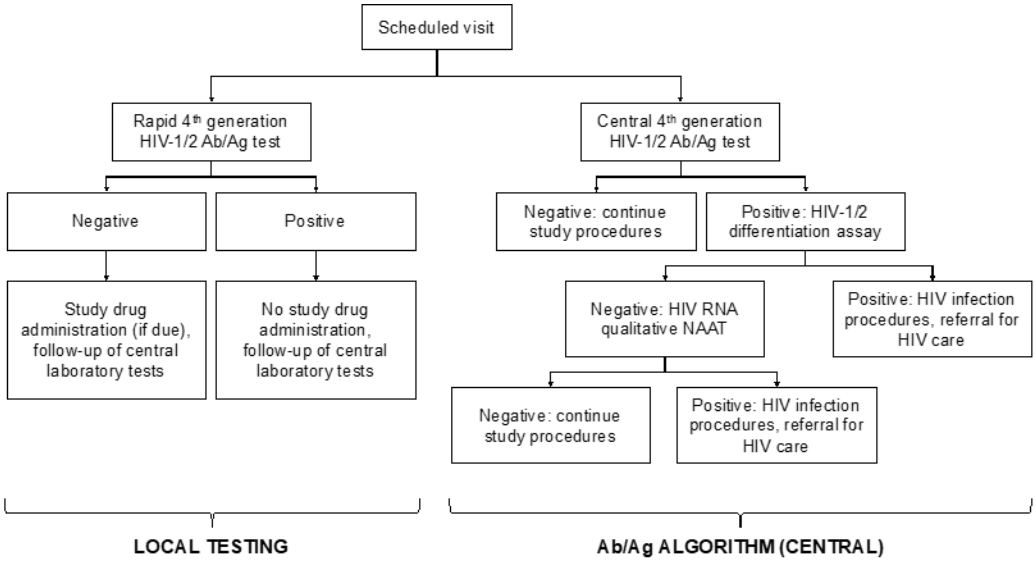
The three voting members of the HIV adjudication committee were infectious disease physician-scientists from HIV Clinical Development who were blinded to randomization assignment:

Jared Baeten, MD, PhD (Senior Vice President, Clinical Development)

Moupali Das, MD, MPH (Vice President, Clinical Development)

Sean Collins, MD (Senior Director, Clinical Development)

Figure S1. HIV-Testing Algorithm



Adapted from CDC HIV testing algorithm.[2-4] Quantitative HIV-1 RNA NAAT, performed for all participants during screening and on Study Day 1, is not depicted in the algorithm for simplicity.

Adherence Counseling and Support

To support participant adherence, study sites developed tailored adherence counseling programs aligned with national and global PrEP guidelines. These programs were adjusted for local settings and participant populations. Pill counts were performed during each visit, and self-reported adherence data were collected through protocol-defined questionnaires. Participants received ongoing adherence counseling, as well as condoms and lubricants at each visit. Participants were considered adherent to lenacapavir if injections were administered within 28 weeks of the prior injection. Participants who delayed injections beyond 28 weeks were required to undergo a repeat baseline HIV testing procedure and receive a reloading dose of oral lenacapavir before resuming injections.

Site-Specific Recruitment Plans

Site-specific recruitment plans were developed to facilitate the recruitment of diverse (race, ethnicity, and gender) study participants at each site. First, we reviewed the local epidemiology based on US CDC data for metropolitan statistical area (including consultation with key scientists and epidemiology experts in local transgender HIV incidence data) in the United States and relevant local HIV incidence/recent HIV infection data in ex-US countries. Then we developed the individual recruitment plans in collaboration with each site investigator and their research team in order to reflect the demographics and the HIV incidence in the local jurisdiction.[5] For example, in a city in the U.S. where HIV incidence in gay, bi, and other men who have sex with men has declined significantly, the decision may be to focus only on enrolling transgender women, who have not had such declines in HIV incidence. Individual plan numbers were designed to add up to the US and global goals for recruitment. For other cities in the U.S. South, for example, where rates in gay, bi, and other men who have sex with men remain high, particularly among persons of color, we focused recruitment on these groups. The study team regularly reviewed site enrollment (weekly during active enrollment) and provided feedback to individual sites to ensure the demographics of focus were being actively enrolled.

Social Harms Reporting and Support for Participants

Study participants were asked about any social harms experienced at every study visit. If a social harm was reported by a participant a case manager or social worker provided counselling and work with the participant to develop a follow-up plan, including referral to appropriate resources. Any new social harms reported were documented in the study case report forms. Sites were also required to document the provided counselling, care, and referral to appropriate resources. The availability of local resources was confirmed with all sites during the site selection process.

If a participant reported intimate partner violence (IPV) during a study follow-up visit all study sites had protocols in place to connect participants with comprehensive services, including legal advice, emotional support, and social assistance.

Excerpts from the PURPOSE 2 Full Statistical Analysis Plan

Analysis of the Primary Efficacy Endpoint

Definition of HIV-1 Infection

Incidence Phase HIV-1 Infection
Identification of prevalent HIV-1 cases in the Incidence Phase necessitates a case definition that allows for the identification and inclusion of acute HIV-1 cases (which may have not yet seroconverted) while minimizing the risk of including participants with false positive HIV-1 testing. To this end, considering the cross-sectional characteristics of this phase, we define HIV-1 cases in the Incidence Phase as those having at least one of the following lab results at the Incidence Phase screening visit:

a. Positive HIV-1/2 differentiation Ab, OR
b. Positive HIV-1 RNA qualitative test, OR
c. HIV-1 RNA quantitative test ≥200 copies/mL.

Notably, HIV-1/2 differentiation and HIV-1 RNA qualitative tests are confirmatory tests per the study protocol's HIV testing procedures and are therefore only performed when central laboratory HIV-1/2 Ab/Ag testing is positive. The use of HIV-1 RNA quantitative test to assess for acute HIV-1 infection is CDC guideline recommended, and HIV-1 RNA quantitative test results of ≥200 copies/mL are unlikely to be a false positive result.[6]

HIV-1 Infection for Randomized Participants

This study engages an HIV adjudication committee who will review potential HIV-1 infection events in the randomized participants. The committee will, in a blinded, consistent, and unbiased manner, adjudicate and confirm both the diagnosis of each HIV-1 infection (identifying false positive HIV-1 cases) and the date of each diagnosis and when necessary, pinpoint the earliest diagnosis date by back-testing archived samples. This process could identify cases with confirmed HIV-1 diagnosis that occur on or prior to Day 1 (i.e., cases where HIV was present at baseline). The roles and responsibilities of the committee are detailed in the HIV Adjudication Committee Charter.

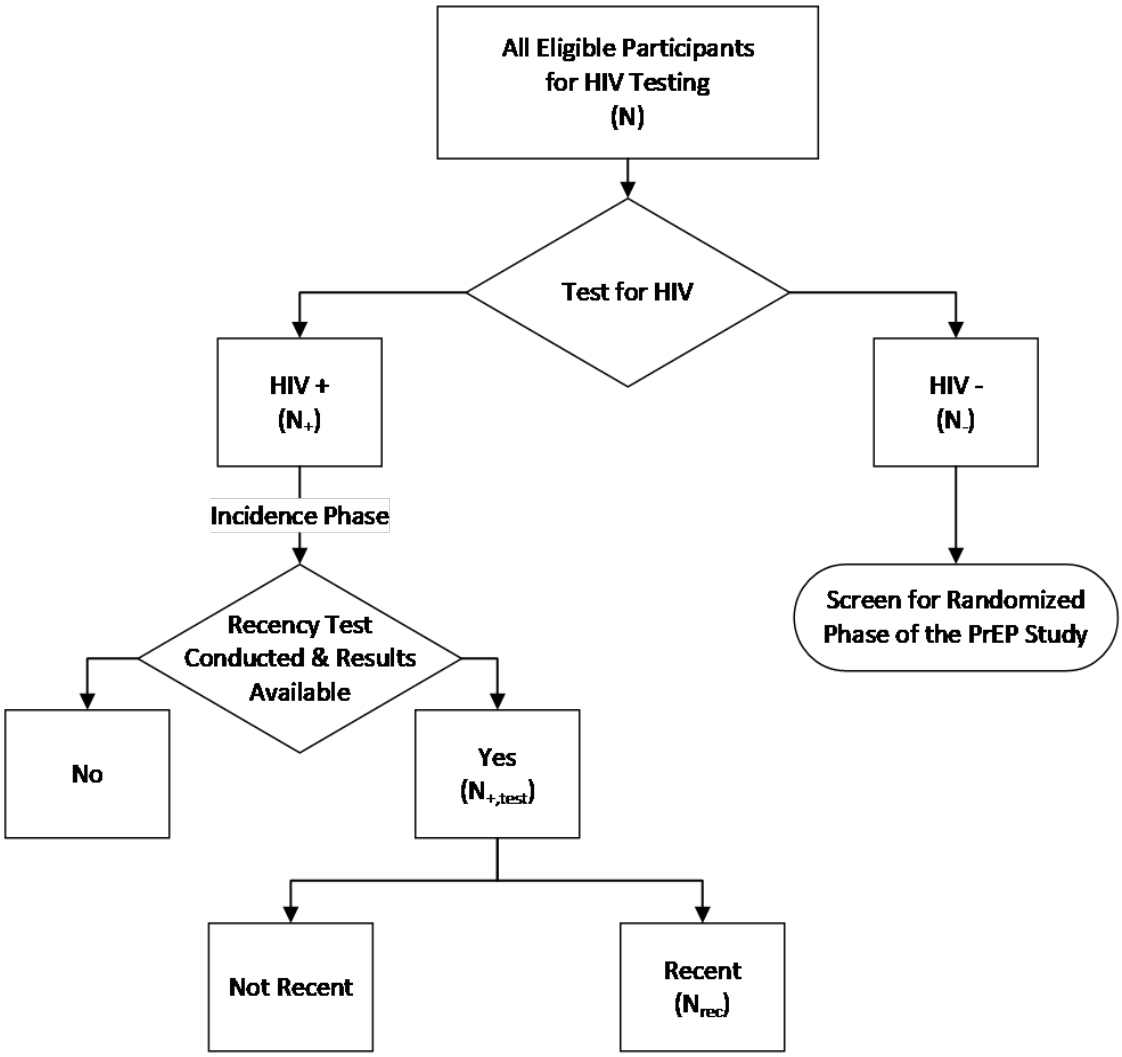
The adjudicated HIV-1 diagnosis and date will be used for all planned reports including the formal interim efficacy analysis (DMC reports), and clinical study reports (primary or any post-primary).

Estimation of HIV-1 Incidence

Incidence Phase

For the Incidence Phase of this study, the bHIV will be reported per 100 PY for the All Screened Set based on a RITA using an HIV1 incidence formula similar to Kassanjee et al 2012[7], adjusting for participants with HIV-1 who may not have recency results (See Figure S2).

Figure S2. A High-Level Screening Schema and Contribution of Participants to the Estimation of the bHIV



The following are the notations.
N: Total number of participants screened
N_-: number of participants who test negative
N_+: number of participants who test positive

$N_{+,test}$: number of positive participants who have recency outcomes available
N_{rec}: number of recent infections as classified by the RITA

The bHIV will be estimated by the formula:

$$\hat{\lambda}_0 = \frac{N_{rec}/(N_{+,test}/N_+) - \beta N_+}{N_-(\Omega - \beta T)}$$

T: cutoff time (eg, 2 years) for the definition of true recent infections
Ω: MDRI
β: FRR

The variance of $\hat{\lambda}_0$ in the log scale $\hat{\sigma}^2_{\log(\hat{\lambda}_0)}$ will be estimated by the delta method, as provided by Gao et al 2021[8] (see below), considering the variance of Ω, β, and the observed counts of N_-, $N_{+,test}$, N_{rec}:

$$\hat{\sigma}^2_{\log(\hat{\lambda}_0)} = \frac{N_{rec}(N_{+,test} - N_{rec})}{N_{+,test}\left(N_{rec} - N_{+,test}\beta\right)^2} + \frac{N}{N_+ N_-} + \sigma_\beta^2 \frac{N_{+,test}(N - N_{+,test})}{N\left(N_{rec} - N_{+,test}\beta\right)^2}$$
$$+ \frac{\sigma_\Omega^2}{(\Omega - \beta T)^2} + \sigma_\beta^2 \left[\frac{N_{+,test}\Omega - N_{rec}T}{(N_{rec} - N_{+,test}\beta)(\Omega - \beta T)}\right]^2$$

The $(1-\alpha) \times 100\%$ confidence interval (CI) for $\log(\lambda_0)$ will be constructed as $\log(\hat{\lambda}_0) \mp z_{\alpha/2}\hat{\sigma}_{\log(\hat{\lambda}_0)}$, and the $(1-\alpha) \times 100\%$ CI for λ_0 will be $\hat{\lambda}_0 \exp\left(\mp z_{\alpha/2}\hat{\sigma}_{\log(\hat{\lambda}_0)}\right)$. Here $z_{\alpha/2}$ is the $(\alpha/2)$-th upper quantile of the standard normal distribution.

Choice of Recency Assay, Assay Parameters and Algorithm Parameters

The Sedia LAg-EIA will be the primary recency assay as it is the most widely used and has been field validated. The number of recent infections N_{rec} will be classified based on the RITA.[9] A participant, diagnosed with HIV-1, will be counted as a recent infection if the normalized optical density (ODn) is below the 1.5 threshold, provided that the HIV-1 RNA viral load is above the cutoff of 75 copies/mL. Table S1 presents the recency outcome from the RITA.

The ODn threshold of 1.5 has been recommended by the Forum for Collaborative Research Recency Assay Working Group (RAWG) in their closing publication[1], by Duong et al 2015[10], the CDC[11] and the Sedia LAg-EIA package insert.

Although the study's eligibility criteria do not allow people who know that they have acquired HIV-1 to be screened, the RITA includes a viral load cutoff of 75 copies/mL to help prevent the overestimation of bHIV by reducing the number of false recent samples from people living with HIV who are virologically suppressed on antiretroviral therapy. When virologically suppressed people with HIV-1 are inadvertently screened, the avidity of their antibodies can be reduced due

to the limited exposure of the immune system to actively replicating HIV-1 which can then lead to an inaccurate recent infection result in the Sedia LAg-EIA. The viral load cutoff used in the RITA must be above the limit of detection of the immunoassay used for determination of the HIV-1 infection, which is 20 copies/mL. Recency assay parameters (MDRI, FRR, etc.) were calculated for a range of viral load cutoffs by Kassanjee et al 2016[9] and the lowest cutoff above 20 copies/mL, that is, 75 copies/mL was chosen for use in the RITA for this study. If a screened participant with HIV-1 has a viral load lower than or equal to the cutoff, the participant will be considered as not recently infected and will be counted in $N_{+,test}$, regardless of the Sedia LagEIA test result, or whether the Sedia LAg-EIA result is available. If an HIV-1 positive participant's viral load is above the cutoff but the ODn- is missing, the participant will be considered as having undeterminable recency outcome, hence excluded from $N_{+,test}$ and N_{rec} but will be included in N_+. If a participant's viral load is missing, the participant will be excluded from $N_{+,test}$ and N_{rec}, but included in N_+. See Table S1 for details.

Table S1. Recency Outcome from the RITA

	HIV-1 Recency Test ODn		
HIV-1 RNA	≤ 1.50	>1.50	Missing ODn
> 75 copies/mL	Recent	Not Recent	Undeterminable
≤ 75 copies/mL	Not Recent	Not Recent	Not Recent

For the RITA, if a participant's HIV-1 RNA is missing or recency outcome is undeterminable, it will be excluded from $N_{+,test}$, but will still be included in N_+. For participants who may have multiple HIV test visits, only tests done at the first HIV test date at Incidence Screening will be used for determining the recency outcome. For the primary analysis, the assay parameters given by Kassanjee et al 2016[9] will be used for bHIV estimation. The sample size calculation in the protocol was also based on Kassanjee et al 2016[9] with $T = 2$ years for pooled samples.

Table S2. MDRI and FRR (Kassanjee et al, 2016[9], $T = 2$ Years)[a]

Subtype	MDRI		FRR[b]	
	Days	rSE (%)	%	rSE (%)
A	170	17.3	2.7	98.7
B	146	13.1	1.3	98.7
C	163	8.3	1.4	100.3
D	241	22.5	0.0	NA[c]
AE	172.6	9.93	0.0	NA[c]

Source: Assay parameters for subtypes A, B, C and D are from Kassanjee et al 2016[9], parameters for subtype AE are not available in Kassanjee et al 2016[9], and are estimated using R package "inctools" (https://cran.r-project.org/web/packages/inctools/inctools.pdf) based on data from Klock et al 2020[12].

[a] Based on the Sedia LAg-EIA and RITA cutoffs in Table S1 (i.e., an infection classified as recent if ODn ≤ 1.5 and HIV-1 RNA viral load > 75 copies/mL).

[b] For untreated participants.

[c] For FRR=0%, rSE cannot be calculated; in this case, a standard error (instead of rSE) of zero will be used in the bHIV calculations.

Note: The Sedia LAg-EIA package insert refers to an MDRI of 130 days (95% CI 118-142, or rSE = 4.7%) and an FRR of <1% for $T = 1$ using ODn cutoff of 1.5 and HIV-1 RNA viral load cutoff of 1000 copies/mL.

Since subtype data will not be available for analysis, we will use country, as a correlate, to estimate the percentage of each subtype instead. Based on a literature review for the geographical distribution of our study sites, we assume all HIV-1 infections from South Africa to be subtype C, all infections from Mexico, United States, Peru, and Argentina to be subtype B, infections from Thailand to be 12% subtype B and 88% subtype AE, and infections from Brazil to be 92% subtype B and 8% subtype C.

The MDRI used in estimating the bHIV for this study will be calculated as the weighted average of the MDRI for the subtypes included in the study. More specifically, let w1, w2, w3, w4, w5, w6, w7 be the proportion of HIV-1 infections from South Africa, Mexico, United States, Peru, Thailand, Argentina, and Brazil, respectively. The distribution of the three subtypes is:

Subtype B: w2+w3+w4+0.12w5+w6+0.92w7
Subtype C: w1+0.08w7
Subtype AE: 0.88w5

Let Ω_B, Ω_C, Ω_{AE} be the MDRI for the subtypes B/C/AE, and $\sigma_{\Omega,B}$, $\sigma_{\Omega,C}$, $\sigma_{\Omega,AE}$ be the corresponding standard errors, which will be computed as the product of MDRI and the rSE of the MDRI in
Table S. The overall MDRI will be estimated by

$$\Omega = (w_2 + w_3 + w_4 + 0.12w_5 + w_6 + 0.92w_7)\Omega_B + (w_1 + 0.08w_7)\Omega_C + 0.88w_5\Omega_{AE}.$$

And the standard error of the overall MDRI will be estimated by

$$\sigma_\Omega = \sqrt{(w_2 + w_3 + w_4 + 0.12w_5 + w_6 + 0.92w_7)^2\sigma_{\Omega,B}^2 + (w_1 + 0.08w_7)^2\sigma_{\Omega,C}^2 + (0.88w_5)^2\sigma_{\Omega,AE}^2}.$$

The rSE of the overall MDRI will be calculated as σ_Ω/Ω, reported as a percentage (%).

The overall FRR will be estimated by the weighted average of the FRR for the subtypes. Let β_B, β_C, and β_{AE} be the FRR for the subtypes B/C/AE, and $\sigma_{\beta,B}$, $\sigma_{\beta,C}$, and $\sigma_{\beta,AE}$ be the corresponding standard errors, which will be computed as the product of the FRR and the rSE of the FRR in Table S. The overall FRR will be estimated by

$$\beta = (w_2 + w_3 + w_4 + 0.12w_5 + w_6 + 0.92w_7)\beta_B + (w_1 + 0.08w_7)\beta_C + 0.88w_5\beta_{AE}.$$

And the standard error of the overall FRR will be estimated by

$$\sigma_\beta = \sqrt{(w_2 + w_3 + w_4 + 0.12w_5 + w_6 + 0.92w_7)^2\sigma_{\beta,B}^2 + (w_1 + 0.08w_7)^2\sigma_{\beta,C}^2 + (0.88w_5)^2\sigma_{\beta,AE}^2}.$$

The rSE of the overall FRR will be calculated as σ_β/β, reported as a percentage (%).
It should be noted that the FRR has been shown to be zero[1,9] for antiretroviral therapy (ARV)-treated HIV-1-positive participants but this is a PrEP trial and the ARV-treated participants and those on PrEP at screening should be excluded by the eligibility criteria. Hence,
Table SS2 only lists FRRs for untreated participants. However, the possibility that a few, ARV-treated participants may be screened, cannot be ruled out. For the primary efficacy analysis using $T = 2$ years, we will conservatively use the untreated FRR for all participants in calculating the bHIV.

While Participants are At-Risk of HIV-1 Infection in Study

The HIV-1 incidence will be reported per 100 PY in lenacapavir and F/TDF study drug groups while at-risk of HIV-1 infection in study.

The HIV-1 incidence in lenacapavir and F/TDF study drug groups will be estimated using a method appropriate for a single Poisson rate based on the FAS. The HIV-1 incidence λ_1 will be estimated by the number of HIV-1 infections in study divided by the total follow-up time in study for each arm. Here "in study" includes postbaseline time in study [including the RBP and follow-up time of participants who discontinue the randomized blinded study drug early (regardless of reason) and may receive OL oral PrEP administered via the PK Tail Phase or stopped taking any PrEP during the study].
The exact $(1-\alpha)\times 100\%$ CI for λ_1 will be constructed as follows:[13]

$$(L_l, L_u) = \left(\frac{\chi^2_{2Y,\frac{\alpha}{2}}}{2D}, \frac{\chi^2_{2(Y+1),1-\frac{\alpha}{2}}}{2D}\right).$$

Here (L_l, L_u) is the lower and upper bound of the exact CI. Y is the observed number of infections, D is the total follow-up time, and $\chi^2_{\nu,\alpha}$ is the chi-square quantile for lower tail probability α on ν degrees of freedom. In the case where $Y = 0$, the lower bound L_l will be set to 0.

The standard error of the incidence estimate $\hat{\lambda}_1$ in the log scale $\hat{\sigma}_{\log(\hat{\lambda}_1)}$ will be estimated by $1/\sqrt{Y}$, based on the Poisson assumption.[8]

Definition of Duration of At-Risk of HIV-1 Infection in Study

Duration of at-risk of HIV-1 infection in the study is defined as the time from Day 1 (first dose date) through the last at-risk of HIV-1 infection date in the study (last at-risk of HIV-1 infection date in study – Day 1 date +1).

Duration of time at-risk of HIV-1 infection in the study will be summarized, in weeks, using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, maximum and total person-years) and as the number and percentage of participants at risk of HIV-1 infection in study for specified periods, i.e., ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 13 weeks (91 days), ≥ 26 weeks (182 days), ≥ 39 weeks (273 days), ≥ 52 weeks (364 days), ≥ 65 weeks (455 days), ≥ 78 weeks (546 days), ≥ 91 weeks (637 days), ≥ 104 weeks (728 days), ≥ 117 weeks (819 days), ≥ 130 weeks (910 days), etc.

Intercurrent Events

On December 20, 2021, the administration of lenacapavir SC injection was put on clinical hold, pausing the screening, and enrollment of new participants and continued dosing of injectable lenacapavir for ongoing participants. Ongoing participants in the study, treated on or prior to December 21, 2021, whose next SC injection visit occurred during the clinical hold were either switched to open-label F/TDF or open-label F/TAF prior to Protocol Amendment 2, or switched to blinded oral weekly LEN/PTM bridging study drug (instead of lenacapavir SC or placebo injections every 6 months) according to their original randomized study drug assignment after Protocol Amendment 2.

This clinical hold and early discontinuation of study drug will be considered intercurrent events during the RBP. However, consistent with the ITT approach, these intercurrent events will be handled with a treatment policy strategy for the primary efficacy evaluations, meaning that participant outcomes will be included in the analysis whether or not the intercurrent event occurred.

General Considerations of Analyses of the Primary Efficacy Endpoint

A formal interim efficacy analysis will be performed after 50% of participants enrolled have completed at least 52 weeks of follow-up in the study or have prematurely discontinued from the

study (50th percentile randomized participant has reached Week 52 or prematurely discontinued from the study).

Efficacy Evaluations

A high-level description of efficacy objectives and analyses is presented in Table S3 to frame the efficacy analysis plan detailed in later sections.

Table S3. Summary for Key (Alpha-Controlled) Efficacy Evaluations

Objectives	Analysis Set	Population-Level Summary	Analysis Period & Intercurrent Events (ICE)
Primary: To evaluate the efficacy of lenacapavir in reducing the risk of HIV-1 infection	Incidence Phase: All Screened Set Randomized groups: Full Analysis Set (FAS)	Rate Ratio: LEN/bHIV	bHIV: In the Incidence Phase prior to the first dose date & No applicable ICE LEN: In study regardless of ICEs (the clinical hold and early discontinuation of study drug); a treatment policy strategy
Secondary: To evaluate the comparability of lenacapavir to TVD	FAS	Rate Difference: LEN-TVD	LEN and TVD: In study regardless of ICEs (the clinical hold and early discontinuation of study drug); a treatment policy strategy
Secondary: To evaluate the superiority of lenacapavir to TVD	FAS	Rate Ratio: LEN/TVD	LEN and TVD: In study regardless of ICEs (the clinical hold and early discontinuation of study drug); a treatment policy strategy)

Multiple Comparisons

Procedures to control the overall Type I error due to multiple efficacy analyses, one due to multiple hypotheses and the other due to one planned interim efficacy analysis, are described in this section.

Multiple Alpha-Controlled Hypotheses

There are 4 alpha-controlled efficacy evaluations planned for this study and the null hypothesis for each one is listed below.

For simplicity, lenacapavir and TVD are used to denote the HIV-1 incidences for the lenacapavir arm and F/TDF arm, respectively.

Table S4. Testing Sequence of Null Hypotheses

Objectives	Null Hypothesis	Interpretation for Rejecting Null Hypothesis
LEN Primary Objectives	H_{01}: lenacapavir / bHIV ≥ 1	HIV-1 incidence in lenacapavir is significantly lower than bHIV
	H_{02}: lenacapavir / bHIV ≥ 0.8	HIV-1 incidence in lenacapavir is significantly and at least 20% lower than bHIV and the point estimate LEN/bHIV ≤ 0.5.
LEN Secondary Objectives	H_{03}: lenacapavir – TVD ≥ 0.8/100PY	HIV-1 incidence in lenacapavir is not substantially greater than F/TDF (LEN efficacy is comparable to F/TDF)
	H_{04}: lenacapavir / TVD ≥ 1	HIV-1 incidence in lenacapavir is significantly lower than F/TDF

The overall Type I error will be controlled at one-sided $\alpha = 0.025$ by following a fixed sequence approach (in the sequential order listed in Table S4).

Alpha Spending for Multiple Analyses (Interim and Primary Analyses)

At the interim analysis, the same sequential approach will be utilized at $\alpha_1 = 0.0026$ (one-sided). The FDA interim stopping criteria are to demonstrate both superiority of lenacapavir versus bHIV, designated H_{02} with the point estimate of $LEN/bHIV \leq 0.5$, and superiority of lenacapavir versus F/TDF, designated H_{04}, at $\alpha_1 = 0.0026$. The interim analysis will serve as the primary analysis if the trial meets the stated criteria and stops early.

If the RBP continues to the primary analysis, the null hypotheses H_{01}, H_{02}, H_{03} and H_{04} will be tested sequentially, with boundaries derived based on the Bonferroni method; at level $\alpha_2 = 0.025 - \alpha_1 = 0.025 - 0.0026 = 0.0224$. The FDA success criteria for the primary analysis are to demonstrate superiority of lenacapavir versus bHIV, designated H_{02} with the point estimate of $LEN/bHIV \leq 0.5$, and comparability of lenacapavir to F/TDF, designated H_{03}, at $\alpha_2 = 0.0224$.

If adequate safety and efficacy of lenacapavir is demonstrated, participants will be given the option to transition to the lenacapavir open-label extension phase of the trial once the RBP is stopped.

Efficacy Evaluations for Key (Alpha-Controlled) Statistical Hypotheses

Primary Efficacy Evaluations (Comparison with bHIV)

The primary efficacy evaluation is a comparison of the observed HIV-1 incidence in the lenacapavir arm during the RBP to the bHIV. The statistical hypotheses are:

Null hypothesis: H_{01}: $\text{LEN/bHIV} \geq 1.0$

Alternative hypothesis: $\text{LEN/bHIV} < 1.0$

It will be concluded that HIV-1 incidence in the lenacapavir group is significantly lower compared to the bHIV if the null hypothesis is rejected in favor of the alternative hypothesis, at an overall 1-sided significance level of 0.025.

Additionally for the primary analysis, the success criteria for the US FDA regulatory review is defined as the HIV-1 incidence rate ratio of at least 20% reduction in the lenacapavir study drug group compared with the bHIV estimated in the Incidence Phase, formulated as the key alpha-controlled H_{02} (gated on rejection of H_{01}) with a point estimate of LEN/bHIV ≤ 0.5 and comparability to F/TDF formulated as the key alpha-controlled H_{03}.

Methods for the Primary Efficacy Evaluations

The incidence rate ratio of the lenacapavir group ($\hat{\lambda}_1$) over the bHIV ($\hat{\lambda}_0$) will be calculated, and the associated CI will be estimated using the delta method as provided by Gao et al 2021[8] (see below):

Let R denote the incidence rate ratio λ_1/λ_0. In log scale, $\log R$ (ie, $\log(\lambda_1) - \log(\lambda_0)$) can be estimated by $\log \hat{R} = \log(\hat{\lambda}_1) - \log(\hat{\lambda}_0)$. $\log \hat{R}$ has an asymptotic normal distribution[8]:

$$\log \hat{R} \sim N\left(\log R\,, \hat{\sigma}^2_{\log(\hat{\lambda}_0)} + \hat{\sigma}^2_{\log(\hat{\lambda}_1)}\right).$$

The $(1-\alpha) \times 100\%$ CI for $\log R$ can then be constructed as $\log(\hat{\lambda}_1) - \log(\hat{\lambda}_0) \mp z_{\alpha/2}\sqrt{\hat{\sigma}^2_{\log(\hat{\lambda}_0)} + \hat{\sigma}^2_{\log(\hat{\lambda}_1)}}$, and the $(1-\alpha) \times 100\%$ CI for the incidence rate ratio R will be $\frac{\hat{\lambda}_1}{\hat{\lambda}_0}\exp\left(\mp z_{\alpha/2}\sqrt{\hat{\sigma}^2_{\log(\hat{\lambda}_0)} + \hat{\sigma}^2_{\log(\hat{\lambda}_1)}}\right)$. Here $z_{\alpha/2}$ is the $(\alpha/2)$-th upper quantile of the standard normal distribution.

The test statistic $Z = \frac{\log \hat{R} - \log R_0}{\sqrt{\hat{\sigma}^2_{\log(\hat{\lambda}_0)} + \hat{\sigma}^2_{\log(\hat{\lambda}_1)}}}$ will be used for hypothesis testing, where R_0 will be set to 1 for testing H_{01} and set to 0.8 for testing H_{02}. The 1-sided p-value will be calculated based on the asymptotic normal distribution of Z.

If the number of HIV-1 infections diagnosed in the lenacapavir group is zero, a plausible scenario especially for the interim analysis or the subgroup analysis, the estimated HIV-1 incidence $\hat{\lambda}_1$ will be zero, and the methods specified above would fail. In this case, the CI and the 1-sided p-value will be estimated using a likelihood-based method proposed by Shao et al 2024.[14]

Secondary Efficacy Evaluations (Comparison with F/TDF)

Analysis Methods for Difference in HIV-1 Incidence Rates

Difference in HIV-1 incidence rates will evaluate comparability of lenacapavir relative to F/TDF, that is, null hypothesis H_{03}. Rejection of this hypothesis will support a conclusion that the HIV-1 incidence in the lenacapavir arm is comparable to F/TDF. In order to test this hypothesis, a CI will be constructed using a hybrid approach recommended by Li et al 2011 with an additional modification to use the exact CI for the single Poisson rate parameter instead of the approximate CI recommended.[15]

Let $\hat{\lambda}_1, \hat{\lambda}_2$ be the estimates of the HIV-1 incidence rates in the two study drug groups, and let $(l_1, u_1), (l_2, u_2)$ be the exact $(1-\alpha) \times 100\%$ CIs for single Poisson rates[13]:

$$(l_i, u_i) = \left(\frac{\chi^2_{2Y_i, \alpha/2}}{2D_i}, \frac{\chi^2_{2(Y_i+1), 1-\alpha/2}}{2D_i}\right), i = 1,2$$

where Y_i's are the observed numbers of infections and D_i's are the total follow-up times for each of the study drug groups, respectively, and $\chi^2_{\nu,\alpha}$ is the chi-square quantile for lower tail probability α on ν degrees of freedom. In the case where $Y_i = 0$, the lower bound l_i will be set to 0.

Then, the hybrid $(1-\alpha) \times 100\%$ CI for the incidence rate difference $\lambda_1 - \lambda_2$ is given by Equations (4) and (5) in Li et al 2011[15] as follows:

$$L = \hat{\lambda}_1 - \hat{\lambda}_2 - \sqrt{\left(\hat{\lambda}_1 - l_1\right)^2 + \left(u_2 - \hat{\lambda}_2\right)^2},$$

$$U = \hat{\lambda}_1 - \hat{\lambda}_2 + \sqrt{\left(u_1 - \hat{\lambda}_1\right)^2 + \left(\hat{\lambda}_2 - l_2\right)^2}.$$

It will be concluded that lenacapavir is comparable to F/TDF if U, the upper bound of the CI of the incidence rate difference (LEN – F/TDF), is less than 0.8 per 100 PY.

After we get the CI, we can use the duality of hypothesis testing and CI[16] to get the corresponding p-value. For any specified α, we can compute the upper bound of the $(1-\alpha)\times 100\%$ CI, U. Therefore, we can view U as a decreasing function of α, ie, view it as $U(\alpha)$. Solve the equation $U(\alpha) = 0.8/100\text{PY}$ for α, then $\alpha/2$ will be the 1-sided p-value.

Analysis Methods for Ratio of HIV-1 Incidence Rates

Ratio of HIV-1 incidence rates will evaluate the relative statistical difference between lenacapavir and F/TDF. The rate ratios of HIV-1 incidence between lenacapavir and F/TDF will be calculated, and the associated CI will be estimated using a generalized model associated with a Poisson distribution and logarithmic link with the study drug group being the main effect.

If the number of infections is zero in any of the experimental groups (LEN or F/TDF), the Poisson model would fail. Therefore, an exact conditional Poisson regression model will be used as the prespecified alternate to the generalized Poisson model specified above.
As specified earlier, H_{04} will be tested sequentially after H_{03} has been rejected.

A supportive analysis for the rate ratios may also be performed using time-to-event analysis methods including Kaplan-Meier estimates and/or the proportional hazards model.

Interim Analysis

Timing

A formal interim efficacy analysis will be performed when 50% of participants have completed Week 52 or have prematurely discontinued from the study (50th percentile randomized participant has reached Week 52 or prematurely discontinued from the study).

If the interim analysis of efficacy data leads to stopping the RBP of the study, either for efficacy or futility, then it will serve as the primary analysis. Otherwise, the unblinded primary analysis will be conducted when all participants have a minimum of 52 weeks (1 year) of follow-up in the RBP of the study or permanent discontinuation of study (whichever occurs first) after randomization.

Efficacy Boundary

At the interim analysis, an alpha of 0.0026 (1-sided) will be spent, based on the Bonferroni's method, and the remaining alpha at the primary analysis will be 0.025-0.0026=0.0224.

At the interim analysis, given the FDA interim stopping criteria, the RBP of the trial will stop early if superiority of lenacapavir over bHIV, designated H02 with the point estimate of $LEN/bHIV \leq 0.5$, and over F/TDF, designated H04, both at $\alpha_1 = 0.0026$ are demonstrated. The interim analysis will serve as the primary analysis if the trial meets the stated criteria and stops early.

Futility Boundary

The study will be stopped if F/TDF is found to be superior to lenacapavir at $\alpha_1 = 0.0026$.

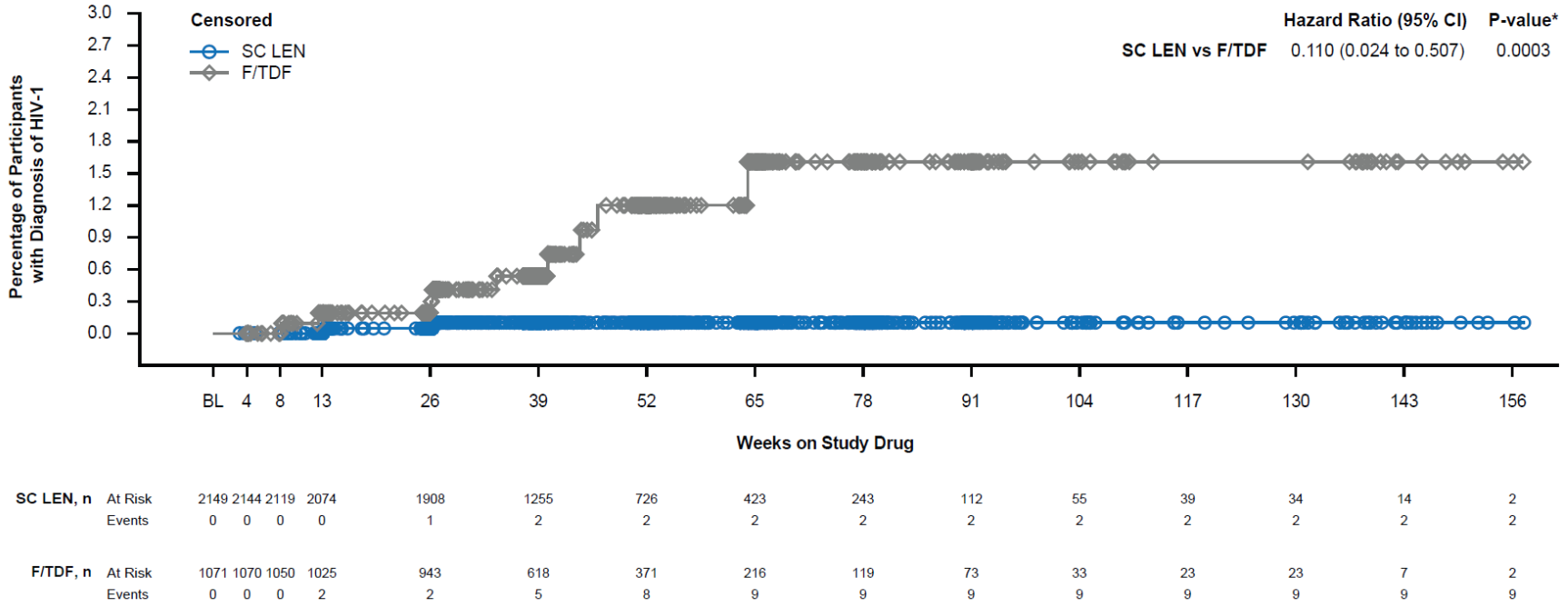
RITA Malperformance

The use of the recency assay and RITA to estimate the bHIV in PrEP studies is a novel approach. The estimate of the bHIV is subject to assay and operational issues. Specifically for the interim analysis, if the point estimate of the RITA based counterfactual bHIV is less than 1.5/100 PY, the estimate of bHIV by the recency assay-based methodology will be deemed as not performing as expected. Gilead expects the bHIV (point estimate) in screened participants in both studies to be at least 3.5/100 PY or higher due to the selection of sites in geographies with high bHIV in eligible people who would benefit from PrEP (PWBP). There exists the possibility of unforeseen factors with operationalizing the RITA methodology in the clinical trial context which may result in RITA estimates that are much lower than expected based on the available estimates of the bHIV in these locations, which we refer to here as RITA malperformance. In the case of RITA malperformance, hypotheses H_{01} and H_{02} will be skipped (no gating or alpha adjustment) at the interim efficacy analysis for testing hypotheses H_{03} and H_{04}. If both hypotheses for testing comparability and superiority to F/TDF are rejected at $\alpha_1 = 0.0026$, the RBP of the study will be stopped, and the study will move to the lenacapavir open-label extension phase in order to provide participants randomized to F/TDF the option for the superior HIV prevention option. Otherwise, the RBP will continue to the primary analysis. This provision serves an important ethical purpose in the study, ensuring that a study arm with inferior efficacy is not continued longer than necessary due to malperformance of the RITA.

Supplementary Results

Figures

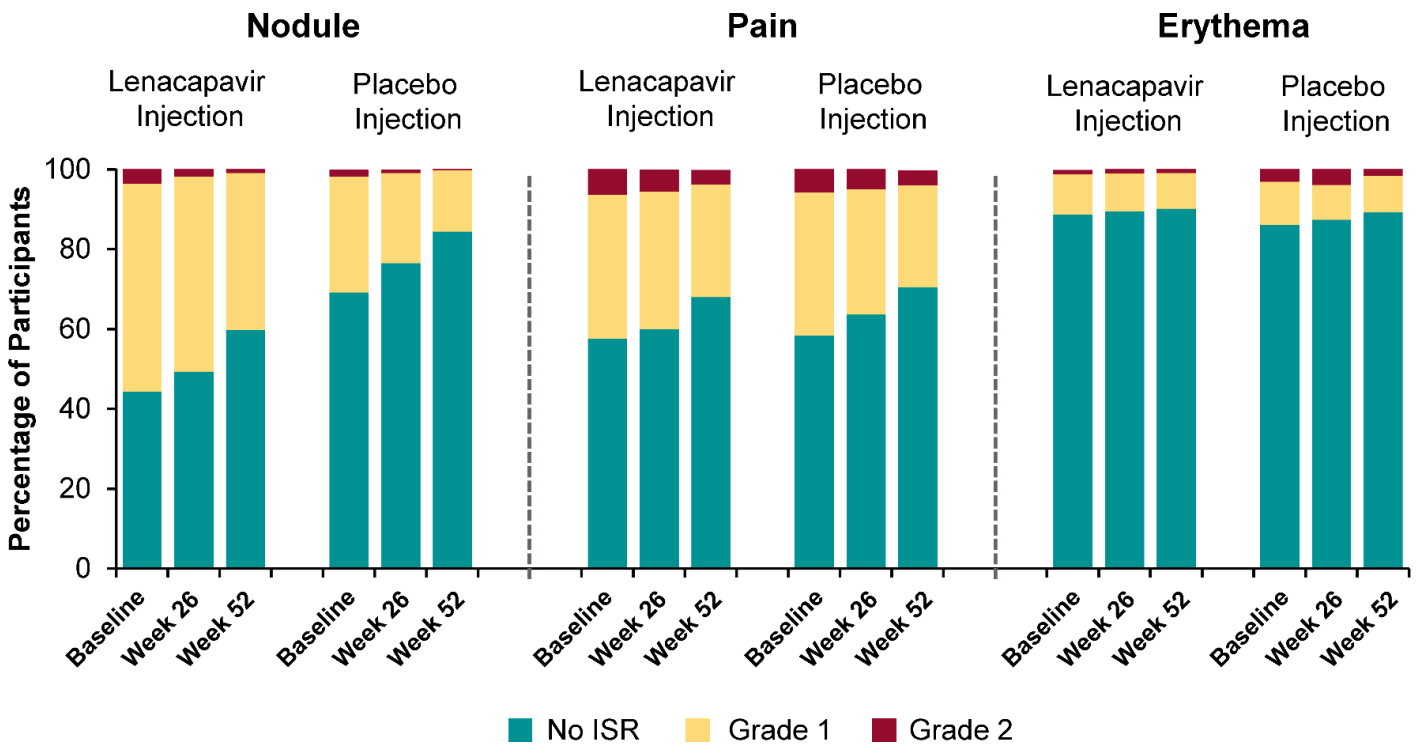
Figure S3. Time from First Dose to HIV-1 Diagnosis



*One-sided Logrank test.

F/TDF denotes emtricitabine-tenofovir disoproxil fumarate, LEN, lenacapavir and SC, subcutaneous. Number of participants at risk calculated at beginning of visit. Participants without an HIV diagnosis were censored at the last at-risk of HIV date defined as date of last post-baseline HIV laboratory test (either rapid, central or other local laboratory tests, including follow up visits).

Figure S4. Injection-Site Reactions (Nodules, Pain, and Erythema)



At each clinical study visit any clinical events, including injection site reactions (ISRs), were elicited. ISRs were then objectively examined (and measured if applicable) by study staff, graded according to the Division of AIDS (DAIDS) Table for Grading the Severity Adverse Events for site reactions to injections and infusions, and documented as adverse events in the eCRF. Adverse events coded according to Medical Dictionary for Regulatory Activities, Version 27.0. Subcutaneous nodules, injection-site pain, and erythema were the most commonly reported injection-site reactions; over the period of study, they occurred in 63.4%, 56.4 %, and 17.3% of participants in the lenacapavir group, respectively, versus 39.2%, 53.4%, and 19.4% of participants given placebo injections; Grade 1 and 2 injection-site reactions are shown, Grade 3 injection-site reactions in the lenacapavir group: n=4 (0.2%) pain, n=3 (0.1%) erythema; F/TDF group: n=1 pain (<0.1%). There were no Grade 3 adverse events of injection-site nodule in either group. Grade 3 injection-site ulcers occurred in n=7 (0.3%) participants in the lenacapavir group and zero participants in the F/TDF group.
Pain mitigation measures including ice or cold compress administration before and after the injection were implemented during the trial. Inappropriate injection technique, especially injection into the dermis rather than the subcutaneous space, was associated with more severe injection-site reactions, such as ulcer formation.
Lenacapavir n: baseline, 2183; Week 26, 1859; Week 52, 744. Placebo n: baseline, 1088; Week 26, 946; Week 52, 379. F/TDF denotes emtricitabine-tenofovir disoproxil fumarate and ISR injection-site reaction.

Tables

Table S5. HIV Test Results for Participants Adjudicated to Have HIV at Baseline

Case	Group	Day	Rapid 4th gen	Central 4th gen	Ab differentiation	Viral load (copies/ml)
1	Lenacapavir	1	Negative	Positive	Negative	67,300,000
		20		Positive	Positive	4340
		111				65,400
		184				<20
		258				Not detected
2	F/TDF	1	Negative	Positive	Negative	90,600,000
		20				104,000
		70				93,000
		117				106,000
		209				<20
3	F/TDF	1	Negative	Negative		207
		8		Negative		1710
		23		Positive	Negative	528
		28	Negative			
		56				Not detected
4	Lenacapavir	1	Negative	Negative		31
		13	Negative			
		21	Negative	Negative		189,000
		29	Negative	Negative		944,000
		77				78,600
		119				166

5	Lenacapavir	1	Negative	Positive	Negative	77,900,000
		21				618
		27				36
		62				27
		126				
6	Lenacapavir	1	Negative	Negative		452
		16		Negative		<20
		32				Not detected
		71				Not detected
		122				Not detected

F/TDF denotes emtricitabine-tenofovir disoproxil fumarate, gen generation, and HIV human immunodeficiency virus.

Table S6. Screening and Baseline Demographics and Clinical Characteristics

	All-Screened Set (N=4634)			Diagnosis of No HIV-1 at Incidence Screening (N=4256)	
	All-Screened Set (N=4634)	Diagnosis of HIV-1 at Incidence Screening		Randomized	
		Yes (N=378)	No (N=4256)	Yes (N=3292)	No (N=964)
Age					
Median (range) — yr	29 (17–80)	28 (18–80)	29 (17–74)	29 (17–74)	29 (17–72)
16 to ≤25 yr — no. (%)	1564 (33.8)	131 (34.7)	1433 (33.7)	1101 (33.4)	332 (34.4)
Sex assigned at birth					
Male	4552 (98.2)	376 (99.5)	4176 (98.1)	3223 (97.9)	953 (98.9)
Female	82 (1.8)	2 (0.5)	80 (1.9)	69 (2.1)	11 (1.1)
Gender identity — no. (%)					
Cisgender man	3585 (77.4)	283 (74.9)	3302 (77.6)	2557 (77.7)	745 (77.3)
Transgender woman	731 (15.8)	77 (20.4)	654 (15.4)	479 (14.6)	175 (18.2)
Transgender man	53 (1.1)	0	53 (1.2)	45 (1.4)	8 (0.8)
Gender nonbinary	252 (5.4)	17 (4.5)	235 (5.5)	200 (6.1)	35 (3.6)
Assigned male at birth	223 (4.8)	15 (4.0)	208 (4.9)	176 (5.3)	32 (3.3)
Assigned female at birth	29 (0.6)	2 (0.5)	27 (0.6)	24 (0.7)	3 (0.3)
Other	13 (0.3)	1 (0.3)	12 (0.3)	11 (0.3)	1 (0.1)
Travesti	7 (0.2)	0	7 (0.2)	6 (0.2)	1 (0.1)
Assigned male at birth	7 (0.2)	0	7 (0.2)	6 (0.2)	1 (0.1)

Assigned female at birth	0	0	0	0	0
Any other	6 (0.1)	1 (0.3)	5 (0.1)	5 (0.2)	0
Assigned male at birth	6 (0.1)	1 (0.3)	5 (0.1)	5 (0.2)	0
Assigned female at birth	0	0	0	0	0
Sexual orientation — no. (%)[*]					
Straight/heterosexual	366 (8.0)	37 (9.9)	329 (7.8)	216 (6.6)	113 (11.9)
Gay	3388 (73.7)	298 (79.5)	3090 (73.2)	2451 (75.0)	639 (67.1)
Lesbian	3 (<0.1)	0	3 (<0.1)	2 (<0.1)	1 (0.1)
Bisexual	690 (15.0)	34 (9.1)	656 (15.5)	494 (15.1)	162 (17.0)
Other	149 (3.2)	6 (1.6)	143 (3.4)	105 (3.2)	38 (4.0)
Pansexual	93 (2.0)	4 (1.1)	89 (2.1)	73 (2.2)	16 (1.7)
Homosexual	13 (0.3)	1 (0.3)	12 (0.3)	6 (0.2)	6 (0.6)
Queer	35 (0.8)	1 (0.3)	34 (0.8)	23 (0.7)	11 (1.1)
Any other	8 (0.2)	0	8 (0.2)	3 (<0.1)	5 (0.5)
Race overall — no. (%)[†]					
Asian	519 (11.2)	30 (8.0)	489 (11.5)	414 (12.6)	75 (7.8)
Black[‡]	1965 (42.5)	261 (69.2)	1704 (40.2)	1241 (37.8)	463 (48.1)
Indigenous or Indigenous ancestry[§]	670 (14.5)	37 (9.8)	633 (14.9)	499 (15.2)	134 (13.9)
White	1374 (29.7)	40 (10.6)	1334 (31.4)	1073 (32.7)	261 (27.1)
Other and other multiracial[¶]	93 (2.0)	9 (2.4)	84 (2.0)	55 (1.7)	29 (3.0)
Ethnicity — no. (%)[#]					
Hispanic or Latine	2822 (60.9)	169 (44.7)	2653 (62.4)	2062 (62.7)	591 (61.3)

Not Hispanic or Latine	1811 (39.1)	209 (55.3)	1602 (37.6)	1229 (37.3)	373 (38.7)
Screening weight					
No.**	3873	28	3845	3291	554
Median (range) — kg	75.1 (39.1–210.8)	71.2 (44.5–97.1)	75.1 (39.1–210.8)	75.2 (39.1–210.8)	74.4 (41.5–163.8)
Screening height					
No.**	3862	18	3844	3291	553
Median (range) — cm	173.0 (123.0–200.7)	174.0 (167.0–183.0)	173.0 (123.0–200.7)	173.0 (123.0–200.7)	172.0 (149.0–200.0)
Screening body mass index					
No.**	3862	18	3844	3291	553
Median (range) — kg/m^2	25.1 (14.4–89.3)	22.9 (14.8–32.1)	25.1 (14.4–89.3)	25.1 (14.4–89.3)	25.3 (15.2–60.2)
Screening waist circumference					
No.**	3863	27	3836	3288	548
Median (range) — cm	86.0 (52.6–175.3)	81.0 (61.0–101.0)	86.0 (52.6–175.3)	86.3 (55.0–175.3)	85.1 (52.6–146.0)
Highest education level					
Did not attend primary school	4 (<0.1)	0	4 (<0.1)	2 (<0.1)	2 (0.2)
Some primary school education	43 (1.0)	7 (2.5)	36 (0.9)	22 (0.7)	14 (1.6)
Primary school complete	162 (3.7)	8 (2.8)	154 (3.7)	116 (3.5)	38 (4.4)
Some secondary school education	531 (12.0)	60 (21.2)	471 (11.4)	376 (11.4)	95 (11.1)
Secondary school degree complete	1517 (34.3)	116 (41.0)	1401 (33.8)	1081 (32.9)	320 (37.5)
Some college or university degree	2168 (49.0)	92 (32.5)	2076 (50.1)	1691 (51.4)	385 (45.1)
Missing**	209	95	114	4	110

Needs help with completion of electronic questionnaire					
Yes	435 (11.2)	3 (13.0)	432 (11.2)	363 (11.0)	69 (12.4)
No	3434 (88.8)	20 (87.0)	3414 (88.8)	2925 (89.0)	489 (87.6)
Missing**	765	355	410	4	406
History of syphilis, rectal gonorrhea, or rectal chlamydia in the past 24 weeks					
Yes	570 (12.3)	41 (10.8)	529 (12.4)	404 (12.3)	125 (13.0)
No	4064 (87.7)	337 (89.2)	3727 (87.6)	2888 (87.7)	839 (87.0)
Condomless receptive anal sex with ≥2 partners in the last 12 weeks					
Yes	4450 (96.0)	371 (98.1)	4079 (95.8)	3195 (97.1)	884 (91.7)
No	184 (4.0)	7 (1.9)	177 (4.2)	97 (2.9)	80 (8.3)
Self-reported use of stimulants with sex in the last 12 weeks					
Yes	1111 (24.0)	74 (19.6)	1037 (24.4)	768 (23.3)	269 (27.9)
No	3523 (76.0)	304 (80.4)	3219 (75.6)	2524 (76.7)	695 (72.1)

BMI denotes body mass index.
Unavailable or missing data were excluded from the calculation of percentage.
* Thirty-eight participants chose not to disclose their sexual orientation in the all-screened cohort.
† Race data were unavailable for 13 participants in the all-screened cohort.
‡ Black included all participants who identified as Black or of Black ancestry: Black, Black/White, Black/Pardo, Black/Brown, Black/Colored, Black/American Indian or Alaskan Native, Black/Asian, and Black/Native Hawaiian or Pacific Islander.
§ American Indian or Alaskan 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.
‖ Other included: Asian/White, Colored, Pardo, White/Brown, multiracial any other, and not multiracial other.
Ethnicity data were unavailable for one participant in the all-screened cohort.
** Missing (weight, height, BMI, waist circumference, education level, and help with electronic questionnaire) when data collection was not required at Incidence Screening.

Table S7. Time at Risk of HIV in the Study and Retention Based on Attending Study Visit and Receiving HIV Testing

Time At-Risk of HIV in Study			
	Lenacapavir (N=2179)	**F/TDF (N=1086)**	**Total (N=3265)**
Duration of time at-risk of HIV, weeks			
No.	2149	1071	3220
Mean (SD)	47.1 (23.9)	47.1 (25.2)	47.1 (24.3)
Median	39.4	39.3	39.4
Q1, Q3	30.7, 56.0	27.9, 55.6	30.2, 55.6
Min, max	3.1, 157.4	3.9, 157.3	3.1, 157.4
Cumulative duration of time at-risk of HIV, person-years	1938.1	966.5	2904.6

Retention by Visit						
	Lenacapavir		**F/TDF**		**Total**	
	Expected — no.	**Actual — no. (%)**	**Expected — no.**	**Actual — no. (%)**	**Expected — no.**	**Actual — no. (%)**
Baseline	2183	2183 (100.0)	1088	1088 (100.0)	3271	3271 (100.0)
Week 4	2153	2110 (98.0)	1070	1046 (97.8)	3223	3156 (97.9)
Week 8	2129	2068 (97.1)	1055	1027 (97.3)	3184	3095 (97.2)
Week 13	2098	2060 (98.2)	1038	1017 (98.0)	3136	3077 (98.1)
Week 26	2010	1882 (93.6)	991	952 (96.1)	3001	2834 (94.4)
Week 39	1563	1472 (94.2)	789	749 (94.9)	2352	2221 (94.4)
Week 52	856	793 (92.6)	421	398 (94.5)	1277	1191 (93.3)
Week 65	476	434 (91.2)	251	230 (91.6)	727	664 (91.3)
Week 78	261	232 (88.9)	135	123 (91.1)	396	355 (89.6)
Week 91	119	105 (88.2)	75	72 (96.0)	194	177 (91.2)
Week 104	39	35 (89.7)	30	28 (93.3)	69	63 (91.3)
Week 117	28	26 (92.9)	23	23 (100.0)	51	49 (96.1)

Week 130	28	20 (71.4)	23	19 (82.6)	51	39 (76.5)
Week 143	18	0	19	0	37	0
Week 156	2	0	4	0	6	0

F/TDF denotes emtricitabine–tenofovir disoproxil fumarate, HIV, human immunodeficiency virus, and Q quartile.

Denominator for percentages is the number of participants expected at each visit. Expected at baseline is the number of participants treated. Expected at postbaseline is the number of participants who were treated and had potential to be followed up on or beyond the upper limit of the clinical visit window (based on their first dose date) and did not discontinue the randomized blinded study phase prior to the upper limit of the clinical visit window. In addition, participants who had a RAPID test or HIV laboratory test visit were also counted as expected participants at the visit. Actual is defined as the number of participants who had an actual HIV test visit for the visit (based on visit labels of labs or case report forms). Laboratory data up to final data extraction date were included.

Table S8. Adherence

Category	Lenacapavir — no.	Lenacapavir (%)	F/TDF — no.	F/TDF (%)
Number of participants expected to receive Week 26 / SC injection 2	1912		952	
On-time SC injection ≤14 days	1729	90.4	877	92.1
< –14 days	2	0.1	4	0.4
–14 to –8 days	12	0.6	9	0.9
–7 to 7 days	1643	85.9	826	86.8
8 to 14 days	72	3.8	38	4.0
Late SC injection >14 days	81	4.2	40	4.2
Did not receive SC injection	102	5.3	35	3.7
Number of participants expected to receive Week 52 / SC injection 3	727		368	
On-time SC injection ≤14 days	678	93.3	338	91.8
< –14 days	4	0.6	4	1.1
–14 to -8 days	13	1.8	4	1.1
–7 to 7 days	615	84.6	305	82.9
8 to 14 days	46	6.3	25	6.8
Late SC injection >14 days	32	4.4	16	4.3
Did not receive SC injection	17	2.3	14	3.8

F/TDF denotes emtricitabine–tenofovir disoproxil fumarate, RBP Randomized Blinded Phase, and SC subcutaneous.
Data show adherence to SC lenacapavir or placebo injection visits for participants randomized and treated after the clinical hold lift. Projected SC lenacapavir or placebo injection visit date is the previous injection visit date plus 26 weeks (182 days). Expected to receive an SC injection includes participants with the potential to be followed up on or beyond the upper limit of the clinical injection visit window (previous SC injection date +189 days [26+1 weeks]) and didn't permanently discontinue RBP prior to upper limit of the protocol clinical injection visit window. Participants with an SC injection at a visit also counted as expected at the visit. Injections are considered received if any injection dose is administered, including partial or incomplete injections. Clinical hold period includes December 21, 2021, through May 16, 2022.

Table S9. Clinical Hold

	Lenacapavir (N=2183)	F/TDF (N=1088)
RBP potentially impacted by clinical hold — no. (%)	59 (2.7)	33 (3.0)
Diagnosis of HIV-1 during clinical hold	0	0
Received oral study drug for clinical hold — no. (%)	59 (2.7)	33 (3.0)
Resumed RBP study drug	40 (1.8)	25 (2.3)
Did not resume RBP study drug	19 (0.9)	8 (0.7)
Received open-label oral F/TDF	3 (0.1)	1 (<0.1)
Resumed RBP study drug	2 (<0.1)	0
Did not resume RBP study drug	1 (<0.1)	1 (<0.1)
Received open-label oral F/TAF	17 (0.8)	15 (1.4)
Resumed RBP study drug	15 (0.7)	11 (1.0)
Did not resume RBP study drug	2 (<0.1)	4 (0.4)
Received open-label oral F/TDF and open-label F/TAF	0	1 (<0.1)
Resumed RBP study drug	0	1 (<0.1)
Did not resume RBP study drug	0	0
Received blinded oral weekly lenacapavir/placebo-to-match bridging	39 (1.8)	16 (1.5)
Resumed RBP study drug injections	23 (1.1)	13 (1.2)

Did not resume RBP study drug injections	16 (0.7)	3 (0.3)

F/TDF denotes emtricitabine–tenofovir disoproxil fumarate, F/TAF emtricitabine–tenofovir alafenamide, HIV human immunodeficiency virus, and RBP Randomized Blinded Phase.
Screening (Incidence or RBP), randomization, or first dose was interrupted by the clinical hold for 18 participants; nine re-screened. There were no HIV-1 diagnoses during re-screening.
RBP Potentially Impacted by Clinical Hold includes participants first dosed on or prior to December 21, 2021, who 1) received oral study drug during clinical hold or 2) permanently discontinued RBP study drug with reason of clinical hold.

Table S10. The Incidence of Laboratory-Diagnosed N. gonorrhoeae, C. trachomatis

Number of STI Events/Person-Years of Follow-Up (Incidence Rate per 100 Person-Years)	Lenacapavir (N=2096)	F/TDF (N=1036)
Gonorrhea or chlamydia	1504/1931.0 (77.9)	668/962.1 (69.4)
Rectal	889/1930.9 (46.0)	388/962.1 (40.3)
Pharyngeal	426/1930.8 (22.1)	216/961.4 (22.5)
Urethral (urine)	189/1929.1 (9.8)	64/958.5 (6.7)
Gonorrhea	789/1931.0 (40.9)	352/962.1 (36.6)
Rectal	382/1930.9 (19.8)	165/962.1 (17.1)
Pharyngeal	350/1930.8 (18.1)	164/961.4 (17.1)
Urethral (urine)	57/1929.1 (3.0)	23/958.5 (2.4)
Chlamydia	715/1931.0 (37.0)	316/962.1 (32.8)
Rectal	507/1930.9 (26.3)	223/962.1 (23.2)
Pharyngeal	76/1930.8 (3.9)	52/961.4 (5.4)
Urethral (urine)	132/1929.1 (6.8)	41/958.5 (4.3)

F/TDF denotes emtricitabine–tenofovir disoproxil fumarate and STI sexually transmitted infection.
Full analysis set among participants with any STI laboratory test while at-risk of HIV in study. Based on central and local laboratory test results. Laboratory tests administered at Week 13 and every 13 weeks. STIs while at risk of HIV are defined as any positive results with a laboratory test date after first dose date through 1) diagnosis date for participants with HIV-1 or 2) latest postbaseline HIV laboratory test date (including follow-up visit, local or central laboratory) for participants without HIV-1. Within each STI and anatomic location, participants with >1 positive test result within 14 days of another positive test result were only counted once.

Table S11. The Incidence of Syphilis

Number of Syphilis Events (Incidence Rate per 100 Person-Years)	Lenacapavir (N=2094)	F/TDF (N=1035)
Person-years of follow-up	1931.2	961.1
Syphilis diagnosis		
Yes	273 (14.1)	119 (12.4)
Disease stage		
Primary	8 (0.4)	3 (0.3)
Early latent	175 (9.1)	74 (7.7)
Secondary	26 (1.3)	16 (1.7)
Tertiary	0	0
Late latent	43 (2.2)	11 (1.1)
Other	20 (1.0)	15 (1.6)
Missing	1	0
Status		
New	203 (10.5)	80 (8.3)
Re-infection	69 (3.6)	39 (4.1)
Missing	1	0

F/TDF denotes emtricitabine–tenofovir disoproxil fumarate, HIV human immunodeficiency virus, and STI sexually transmitted infection. Syphilis testing by blood tests was performed locally based on local testing protocols; syphilis diagnosis, disease stage, and disease status are based on the investigator's clinical diagnosis based on the assessment of both clinical signs and symptoms and local laboratory data. Full analysis set among participants with any syphilis evaluation while at-risk of HIV in study. Missing disease stage or status when not collected in investigator documentation. Results have not been adjudicated. Number of reported events = number of unique participants and diagnosis dates (after first dose date) for each disease stage and status. Person-years are sum of all participants' total number of years (1 year = 365.25 days) of follow-up while at-risk of HIV in study between first dose date and either 1) HIV-1 diagnosis date for participants with HIV-1 or 2) latest postbaseline HIV laboratory test date (including follow-up visit, local or central laboratory) for participants without HIV-1. Missing is excluded from incidence-rate calculations.

Table S12. HIV Test Results in Participants Receiving Lenacapavir Who Were Diagnosed with HIV-1

Participant	**A**				**B**				
Week	0	4	8	13	0	4	8	13	26
Rapid Ag/Ab	(–)	(–)	(–)	(+)	(–)	(–)	(–)	(–)	(–)
Central Ag/Ab	(–)	(–)	(–)	(+)	(–)	(–)	(–)	(–)	(+)
HIV-1/2 Ab diff				(HIV-1 +/ HIV-2 –)*					(HIV-1 +/ HIV-2 –)*
Qualitative HIV-1 RNA				(+)					(+)
Quantitative HIV-1 RNA VL, copies/ml†	ND	ND‡	ND‡	934,000	ND			ND‡	14,100
SCA, copies/ml	ND‡	ND‡	4.8‡		ND‡	ND‡	ND‡	ND‡	

* Antibody differentiation intermediate for HIV-1, negative for HIV-2. HIV-1 confirmed by Qualitative RNA and Quantitative RNA

† Lower limit of quantitation, 20 copies per mL

‡ Denotes tests run from archived samples after HIV diagnosis

(–) denotes negative results, (+) denotes positive results, Central Ag/Ab denotes central laboratory fourth-generation antigen/antibody test, HIV denotes human immunodeficiency virus, HIV-1/2 Ab diff denotes HIV-1/2 antibody differentiation assay, ND denotes no HIV-1 RNA detected, Qualitative HIV-1 RNA denotes qualitative HIV-1 RNA test, Rapid Ag/Ab denotes local rapid HIV-1/2 antigen/antibody test, SCA denotes HIV-1 RNA single-copy assay and VL denotes HIV-1 RNA quantitative viral load; blank denotes test not done.

Table S13. Grade 3 or Higher Adverse Events

	Lenacapavir (N=2183)	F/TDF (N=1088)
Participants with any grade 3 or higher treatment-emergent adverse events (excluding injection-site reactions) — no. (%)	91 (4.2)	65 (6.0)
Participants with any grade 3 or higher treatment-emergent adverse events (including injection-site reactions) — no. (%)	104 (4.8)	66 (6.1)
Grade 3 (Severe)	82 (3.8)	59 (5.4)
Grade 4 (Life-Threatening)	18 (0.8)	6 (0.6)
Grade 5 (Death)	4 (0.2)	1 (<0.1)
Blood and lymphatic system disorders	2 (<0.1)	3 (0.3)
Grade 3 (Severe)	2 (<0.1)	3 (0.3)
Lymphopenia	1 (<0.1)	2 (0.2)
Grade 3 (Severe)	1 (<0.1)	2 (0.2)
Anemia	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Sickle cell anemia with crisis	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Cardiac disorders	3 (0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Grade 4 (Life-Threatening)	2 (<0.1)	0
Atrial fibrillation	2 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Grade 4 (Life-Threatening)	1 (<0.1)	0
Acute myocardial infarction	1 (<0.1)	0
Grade 4 (Life-Threatening)	1 (<0.1)	0
Ear and labyrinth disorders	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)

Vertigo	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Endocrine disorders	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Thyrotoxic periodic paralysis	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Gastrointestinal disorders	6 (0.3)	7 (0.6)
Grade 3 (Severe)	4 (0.2)	7 (0.6)
Grade 4 (Life-Threatening)	2 (<0.1)	0
Diarrhea	0	4 (0.4)
Grade 3 (Severe)	0	4 (0.4)
Nausea	0	3 (0.3)
Grade 3 (Severe)	0	3 (0.3)
Abdominal pain lower	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Colitis	1 (<0.1)	0
Grade 4 (Life-Threatening)	1 (<0.1)	0
Colitis ulcerative	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Dyspepsia	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Hemorrhoids	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Strangulated umbilical hernia	1 (<0.1)	0
Grade 4 (Life-Threatening)	1 (<0.1)	0
Toothache	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Vomiting	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)

General disorders and administration-site conditions	15 (0.7)	5 (0.5)
Grade 3 (Severe)	14 (0.6)	3 (0.3)
Grade 4 (Life-Threatening)	0	1 (<0.1)
Grade 5 (Death)	1 (<0.1)	1 (<0.1)
Injection-site ulcer	7 (0.3)	0
Grade 3 (Severe)	7 (0.3)	0
Injection-site pain	4 (0.2)	1 (<0.1)
Grade 3 (Severe)	4 (0.2)	1 (<0.1)
Injection-site erythema	3 (0.1)	0
Grade 3 (Severe)	3 (0.1)	0
Chills	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Death	1 (<0.1)	1 (<0.1)
Grade 5 (Death)	1 (<0.1)	1 (<0.1)
Ill-defined disorder	0	1 (<0.1)
Grade 4 (Life-Threatening)	0	1 (<0.1)
Injection-site dermatitis	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Injection-site edema	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Lithiasis	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Pyrexia	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Hepatobiliary disorders	4 (0.2)	1 (<0.1)
Grade 3 (Severe)	2 (<0.1)	1 (<0.1)
Grade 4 (Life-Threatening)	2 (<0.1)	0
Cholecystitis acute	1 (<0.1)	1 (<0.1)
Grade 3 (Severe)	1 (<0.1)	1 (<0.1)

Hypertransaminasemia	2 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Grade 4 (Life-Threatening)	1 (<0.1)	0
Hepatitis acute	1 (<0.1)	0
Grade 4 (Life-Threatening)	1 (<0.1)	0
Immune system disorders	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Drug hypersensitivity	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Infections and infestations	34 (1.6)	18 (1.7)
Grade 3 (Severe)	31 (1.4)	18 (1.7)
Grade 4 (Life-Threatening)	3 (0.1)	0
Appendicitis	7 (0.3)	6 (0.6)
Grade 3 (Severe)	7 (0.3)	6 (0.6)
Gastroenteritis	3 (0.1)	2 (0.2)
Grade 3 (Severe)	3 (0.1)	2 (0.2)
Hepatitis A	3 (0.1)	1 (<0.1)
Grade 3 (Severe)	3 (0.1)	1 (<0.1)
Abscess limb	3 (0.1)	0
Grade 3 (Severe)	3 (0.1)	0
Cellulitis	2 (<0.1)	0
Grade 3 (Severe)	2 (<0.1)	0
Dengue fever	2 (<0.1)	0
Grade 3 (Severe)	2 (<0.1)	0
Dengue hemorrhagic fever	2 (<0.1)	0
Grade 3 (Severe)	2 (<0.1)	0
Osteomyelitis	1 (<0.1)	1 (<0.1)
Grade 3 (Severe)	1 (<0.1)	1 (<0.1)

Pneumonia	2 (<0.1)	0
Grade 3 (Severe)	2 (<0.1)	0
Pyelonephritis	0	2 (0.2)
Grade 3 (Severe)	0	2 (0.2)
Abdominal infection	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Acute HIV infection	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Anal abscess	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Anorectal human papilloma virus infection	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Bacterial infection	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Complicated appendicitis	1 (<0.1)	0
Grade 4 (Life-Threatening)	1 (<0.1)	0
Encephalitis viral	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Enteritis infectious	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Erysipelas	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Large intestine infection	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Meningoencephalitis viral	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Peritonsillar abscess	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0

Pneumonia bacterial	1 (<0.1)	0
Grade 4 (Life-Threatening)	1 (<0.1)	0
Pyelonephritis acute	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Sepsis	1 (<0.1)	0
Grade 4 (Life-Threatening)	1 (<0.1)	0
Tonsillitis bacterial	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Injury, poisoning, and procedural complications	10 (0.5)	7 (0.6)
Grade 3 (Severe)	8 (0.4)	7 (0.6)
Grade 4 (Life-Threatening)	1 (<0.1)	0
Grade 5 (Death)	1 (<0.1)	0
Road traffic accident	2 (<0.1)	1 (<0.1)
Grade 3 (Severe)	1 (<0.1)	1 (<0.1)
Grade 5 (Death)	1 (<0.1)	0
Abdominal injury	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Alcohol poisoning	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Ankle fracture	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Chest injury	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Craniocerebral injury	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Craniofacial fracture	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Fall	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0

Femur fracture	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Foot fracture	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Foreign body aspiration	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Joint injury	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Muscle strain	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Patella fracture	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Skin abrasion	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Skin laceration	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Subdural hemorrhage	1 (<0.1)	0
Grade 4 (Life-Threatening)	1 (<0.1)	0
Tibia fracture	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Traumatic fracture	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Wound necrosis	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Investigations	6 (0.3)	3 (0.3)
Grade 3 (Severe)	4 (0.2)	3 (0.3)
Grade 4 (Life-Threatening)	2 (<0.1)	0
Creatinine renal clearance decreased	2 (<0.1)	2 (0.2)
Grade 3 (Severe)	2 (<0.1)	2 (0.2)

Blood creatine phosphokinase increased	2 (<0.1)	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Grade 4 (Life-Threatening)	2 (<0.1)	0
Aspartate aminotransferase increased	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Blood triglycerides increased	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Transaminases abnormal	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Metabolism and nutrition disorders	4 (0.2)	4 (0.4)
Grade 3 (Severe)	4 (0.2)	4 (0.4)
Abnormal loss of weight	2 (<0.1)	3 (0.3)
Grade 3 (Severe)	2 (<0.1)	3 (0.3)
Dehydration	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Dyslipidemia	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Hypertriglyceridemia	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Musculoskeletal and connective tissue disorders	3 (0.1)	1 (<0.1)
Grade 3 (Severe)	2 (<0.1)	1 (<0.1)
Grade 4 (Life-Threatening)	1 (<0.1)	0
Rhabdomyolysis	2 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Grade 4 (Life-Threatening)	1 (<0.1)	0
Bone lesion	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Fibromyalgia	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0

Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (<0.1)	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Grade 4 (Life-Threatening)	2 (<0.1)	0
Acute myeloid leukemia	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Adenocarcinoma of colon	1 (<0.1)	0
Grade 4 (Life-Threatening)	1 (<0.1)	0
Brain neoplasm	1 (<0.1)	0
Grade 4 (Life-Threatening)	1 (<0.1)	0
Nervous system disorders	6 (0.3)	3 (0.3)
Grade 3 (Severe)	4 (0.2)	3 (0.3)
Grade 4 (Life-Threatening)	1 (<0.1)	0
Grade 5 (Death)	1 (<0.1)	0
Cerebrovascular accident	2 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Grade 5 (Death)	1 (<0.1)	0
Syncope	0	2 (0.2)
Grade 3 (Severe)	0	2 (0.2)
Headache	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Sciatica	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Seizure	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Seizure like phenomena	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Subarachnoid hemorrhage	1 (<0.1)	0
Grade 4 (Life-Threatening)	1 (<0.1)	0

Psychiatric disorders	14 (0.6)	9 (0.8)
Grade 3 (Severe)	8 (0.4)	4 (0.4)
Grade 4 (Life-Threatening)	5 (0.2)	5 (0.5)
Grade 5 (Death)	1 (<0.1)	0
Suicide attempt	7 (0.3)	3 (0.3)
Grade 3 (Severe)	2 (<0.1)	0
Grade 4 (Life-Threatening)	5 (0.2)	3 (0.3)
Suicidal ideation	3 (0.1)	4 (0.4)
Grade 3 (Severe)	2 (<0.1)	3 (0.3)
Grade 4 (Life-Threatening)	1 (<0.1)	1 (<0.1)
Depression	3 (0.1)	1 (<0.1)
Grade 3 (Severe)	2 (<0.1)	1 (<0.1)
Grade 4 (Life-Threatening)	1 (<0.1)	0
Major depression	1 (<0.1)	2 (0.2)
Grade 3 (Severe)	1 (<0.1)	2 (0.2)
Anxiety	0	2 (0.2)
Grade 4 (Life-Threatening)	0	2 (0.2)
Alcohol withdrawal syndrome	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Bipolar disorder	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Completed suicide	1 (<0.1)	0
Grade 5 (Death)	1 (<0.1)	0
Depression suicidal	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Mental disorder	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Psychotic disorder	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Schizophrenia	0	1 (<0.1)

Grade 3 (Severe)	0	1 (<0.1)
Substance abuse	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Substance dependence	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Substance use disorder	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Substance-induced psychotic disorder	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Renal and urinary disorders	4 (0.2)	2 (0.2)
Grade 3 (Severe)	4 (0.2)	2 (0.2)
Glycosuria	1 (<0.1)	1 (<0.1)
Grade 3 (Severe)	1 (<0.1)	1 (<0.1)
Nephrolithiasis	1 (<0.1)	1 (<0.1)
Grade 3 (Severe)	1 (<0.1)	1 (<0.1)
Ureteric stenosis	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Ureterolithiasis	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Reproductive system and breast disorders	0	2 (0.2)
Grade 3 (Severe)	0	2 (0.2)
Priapism	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Testicular mass	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Respiratory, thoracic, and mediastinal disorders	0	3 (0.3)
Grade 3 (Severe)	0	3 (0.3)
Pleural effusion	0	2 (0.2)

Grade 3 (Severe)	0	2 (0.2)
Pneumothorax	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Skin and subcutaneous tissue disorders	2 (<0.1)	1 (<0.1)
Grade 3 (Severe)	2 (<0.1)	1 (<0.1)
Cellulite	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Diabetic foot	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Urticaria	1 (<0.1)	0
Grade 3 (Severe)	1 (<0.1)	0
Social circumstances	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Physical assault	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)
Vascular disorders	1 (<0.1)	2 (0.2)
Grade 3 (Severe)	1 (<0.1)	2 (0.2)
Hypertension	1 (<0.1)	1 (<0.1)
Grade 3 (Severe)	1 (<0.1)	1 (<0.1)
Hypertensive crisis	0	1 (<0.1)
Grade 3 (Severe)	0	1 (<0.1)

DAIDS denotes Division of AIDS, F/TDF emtricitabine-tenofovir disoproxil fumarate, HIV human immunodeficiency virus, MedDRA Medical Dictionary for Regulatory Activities, and SC subcutaneous.

Grade 3 = Severe, 4 = Life-Threatening, 5 = Death; DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. Adverse events coded according to MedDRA Version 27.0. Treatment-emergent events began on or after study drug first dose date up through last exposure date for the randomized blinded study phase after permanent discontinuation of study drug or led to premature study drug discontinuation. Treatment-emergent injection-site reaction to study SC injection (related to study drug/procedure, MedDRA high level term=Injection-Site Reactions) began on or after first SC lenacapavir or placebo injection date. Multiple adverse events were counted only once per participant for the highest severity grade for each system organ class and preferred term. System organ classes were presented alphabetically and preferred terms within system organ classes were presented by decreasing order of the total frequencies.

Table S14. Adverse Events Leading to Premature Study Drug Discontinuation

	Lenacapavir (N=2183)	**F/TDF (N=1088)**
Participants any treatment-emergent adverse events leading to study drug discontinuation (excluding injection-site reactions) — no. (%)	7 (0.3)	7 (0.6)
Participants with any treatment-emergent adverse events leading to study drug discontinuation (including injection-site reactions) — no (%)	32 (1.5)	10 (0.9)
Gastrointestinal disorders	1 (<0.1)	3 (0.3)
Abdominal pain	1 (<0.1)	1 (<0.1)
Nausea	1 (<0.1)	1 (<0.1)
Abdominal pain upper	0	1 (<0.1)
Diarrhea	0	1 (<0.1)
General disorders and administration-site conditions	27 (1.2)	4 (0.4)
Injection-site nodule	17 (0.8)	0
Injection-site pain	8 (0.4)	2 (0.2)
Injection-site induration	2 (<0.1)	0
Injection-site granuloma	1 (<0.1)	0
Injection-site mass	0	1 (<0.1)
Injection-site ulcer	1 (<0.1)	0
Malaise	0	1 (<0.1)
Edema peripheral	1 (<0.1)	0
Infections and infestations	2 (<0.1)	0
Gastroenteritis	1 (<0.1)	0
Onychomycosis	1 (<0.1)	0
Investigations	0	2 (0.2)
Creatinine renal clearance decreased	0	2 (0.2)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (<0.1)	0
Brain neoplasm	1 (<0.1)	0

Nervous system disorders	0	1 (<0.1)
Headache	0	1 (<0.1)
Renal and urinary disorders	0	1 (<0.1)
Nephropathy	0	1 (<0.1)
Skin and subcutaneous tissue disorders	3 (0.1)	0
Rash	1 (<0.1)	0
Urticaria	1 (<0.1)	0
Vasculitic rash	1 (<0.1)	0

F/TDF denotes emtricitabine-tenofovir disoproxil fumarate, MedDRA Medical Dictionary for Regulatory Activities, and SC subcutaneous. Adverse events coded according to MedDRA Version 27.0. Treatment-emergent events began on or after study drug first dose date up through last exposure date for the randomized blinded study phase after permanent discontinuation of study drug, or led to premature study drug discontinuation. Treatment-emergent injection-site reaction to study SC injection (related to study drug/procedure, MedDRA high level term=Injection-Site Reactions) began on or after first SC lenacapavir or placebo injection date. Multiple adverse events were counted only once per participant for the highest severity grade for each system organ class and preferred term. System organ classes were presented alphabetically and preferred terms within system organ classes were presented by decreasing order of the total frequencies.

Table S15. Grade 3 and 4 Laboratory Abnormalities

Laboratory Abnormality — no (%)	**Lenacapavir (N=2183)**	**F/TDF (N=1088)**
Participants with postbaseline value	2153	1071
Grade 3	184 (8.5)	122 (11.4)
Grade 4	59 (2.7)	25 (2.3)
Hemoglobin (decreased)	2149	1070
Grade 3	0	1 (<0.1)
Grade 4	2 (<0.1)	0
Lymphocytes (decreased)	2146	1068
Grade 3	7 (0.3)	2 (0.2)
Grade 4	0	1 (<0.1)
Neutrophils (decreased)	2149	1070
Grade 3	1 (<0.1)	3 (0.3)
Grade 4	1 (<0.1)	0
Platelets (decreased)	2147	1069
Grade 3	1 (<0.1)	1 (<0.1)
Grade 4	2 (<0.1)	0
WBC (decreased)	2149	1070
Grade 3	0	0
Grade 4	0	0
Albumin (decreased)	2153	1071
Grade 3	0	0
Grade 4	0	0
Alkaline phosphatase (increased)	2153	1071
Grade 3	0	1 (<0.1)
Grade 4	0	1 (<0.1)
ALT (increased)	2151	1071
Grade 3	11 (0.5)	5 (0.5)
Grade 4	6 (0.3)	1 (<0.1)

AST (increased)	2153	1071
Grade 3	14 (0.7)	8 (0.7)
Grade 4	7 (0.3)	2 (0.2)
Bicarbonate (decreased)	2151	1071
Grade 3	1 (<0.1)	0
Grade 4	0	0
Corrected calcium (hypercalcemia)	2153	1071
Grade 3	1 (<0.1)	0
Grade 4	1 (<0.1)	0
Corrected calcium (hypocalcemia)	2153	1071
Grade 3	9 (0.4)	2 (0.2)
Grade 4	0	0
Creatine kinase (increased)	2153	1071
Grade 3	38 (1.8)	32 (3.0)
Grade 4	44 (2.0)	18 (1.7)
Creatinine (increased)	2153	1071
Grade 3	12 (0.6)	8 (0.7)
Grade 4	0	2 (0.2)
Creatinine clearance (decreased)	2153	1071
Grade 3	42 (2.0)	38 (3.5)
Grade 4	0	2 (0.2)
Direct bilirubin (hyperbilirubinemia)	2151	1071
Grade 3	12 (0.6)	2 (0.2)
Grade 4	0	0
Lipase (increased)	2152	1071
Grade 3	12 (0.6)	6 (0.6)
Grade 4	2 (<0.1)	1 (<0.1)
Magnesium (hypomagnesemia)	2153	1071
Grade 3	10 (0.5)	1 (<0.1)
Grade 4	0	0

Phosphate (hypophosphatemia)	2153	1071
Grade 3	2 (<0.1)	1 (<0.1)
Grade 4	0	0
Serum glucose (fasting, hyperglycemia)	1974	990
Grade 3	5 (0.3)	3 (0.3)
Grade 4	0	0
Serum Glucose (nonfasting, hyperglycemia, maximum postbaseline grade)	1201	605
Grade 3	4 (0.3)	3 (0.5)
Grade 4	0	1 (0.2)
Serum glucose (hypoglycemia)	2153	1071
Grade 3	2 (<0.1)	5 (0.5)
Grade 4	0	0
Serum potassium (hyperkalemia)	2153	1071
Grade 3	4 (0.2)	1 (<0.1)
Grade 4	1 (<0.1)	1 (<0.1)
Serum potassium (hypokalemia)	2153	1071
Grade 3	0	0
Grade 4	0	0
Serum sodium (hypernatremia)	2153	1071
Grade 3	0	1 (<0.1)
Grade 4	1 (<0.1)	1 (<0.1)
Serum sodium (hyponatremia)	2153	1071
Grade 3	0	0
Grade 4	0	0
Total bilirubin (hyperbilirubinemia)	2153	1071
Grade 3	1 (<0.1)	0
Grade 4	5 (0.2)	1 (<0.1)
Total cholesterol (fasting, hypercholesterolemia)	1786	894
Grade 3	6 (0.3)	0
Grade 4	0	0

Triglycerides (fasting, increased)	1785	894
Grade 3	12 (0.7)	3 (0.3)
Grade 4	1 (<0.1)	0
LDL (fasting, increased)	1784	893
Grade 3	16 (0.9)	6 (0.7)
Grade 4	0	0
Uric acid (hyperuricemia)	2153	1071
Grade 3	1 (<0.1)	2 (0.2)
Grade 4	0	0
Urine glucose (glycosuria)	2153	1070
Grade 3	22 (1.0)	15 (1.4)
Grade 4	0	0
Urine protein (proteinuria)	2153	1070
Grade 3	8 (0.4)	4 (0.4)
Grade 4	0	0
Urine RBC (hematuria, quantitative)	2153	1070
Grade 3	0	0
Grade 4	0	0

ALT denotes alanine aminotransferase, AST aspartate aminotransferase, DAIDS Division of AIDS, F/TDF emtricitabine-tenofovir disoproxil fumarate, LDL low-density lipoprotein, RBC red blood cell, and WBC white blood cell.

Denominator for percentage is the number of participants in safety analysis set with at least one postbaseline laboratory value for the test under evaluation. For nonfasting serum glucose hyperglycemia (which includes unknown fasting status): 1) maximum postbaseline toxicity grades, instead of treatment emergent abnormalities, were summarized, as most participants were fasting at baseline and treatment-emergent flag cannot be derived and 2) were excluded in "Participants with Postbaseline Value" summary as the treatment-emergent flag cannot be derived. Participants counted once for the maximum postbaseline severity for each test. Urinalysis (i.e., urine protein, urine glucose) highest grade is Grade 3. The incidence of any grade creatinine clearance (decreased) was lower in the lenacapavir group (41.4%) compared with the F/TDF group (52.4%). Fasting metabolic assessments are collected at Day 1, Week 26, and every 26 weeks. Severity grades were defined by DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1.

Table S16. PURPOSE 2 in Comparison with Previous PrEP Trials

PrEP trial — no. (%)	Non-White Race	Hispanic/Latine	Cisgender/Gay, Bi, and Other MSM	Transgender Women	Transgender Men	Gender Nonbinary
iPrEx[17]	2068 (83)	1806 (72)	2470 (99)	29 (1)	0	0
IPERGAY[18,*]	34 (9)	-	400 (100)	0	0	0
PROUD[19]	99 (19)	-	543 (100)	1 (< 1)	0	0
DISCOVER[20]	868 (16)[†]	1318 (24)	5313 (99)	74 (1)	0	0
HPTN 083[21,‡]	3283 (72)	2110 (46)	3992 (87)	570 (13)	0	0
PURPOSE 2	2195[§] (67)	2053[‖] (63)	2543 (78)	476 (15)	43 (1)	209 (6)[#]

MSM denotes men who have sex with men, and PrEP preexposure prophylaxis; hyphens in the table denote no data were available for the corresponding baseline characteristic.
* Inclusion criteria were male or transgender female sex among participants who have sex with men; however, no transgender women participants were reported. [†] Race data were not available for eight participants. [‡] Four (<1%) participants preferred not to provide their gender identity; data on race were not available for 20 participants (includes data from Landovitz RJ, personal communication. October 7, 2024). [§] Data on race were not available for 10 participants. [‖] Data on ethnicity were not available for one participant. [#] Nonbinary included n=6 individuals who identified as Travesti (all assigned male at birth) and n=4 individuals who identified as an "Other" gender (all assigned male at birth).

Table S17. Participants in PURPOSE 2 Reflect Global Populations of Cisgender Gay, Bisexual, and Other Men; Transgender Women; Transgender Men; and Gender Nonbinary Individuals Disproportionately Affected by HIV Acquisition and Historically Underrepresented in PrEP Clinical Trials

Category	Example
Disease, problem, or condition under investigation	Prevention of HIV-1 Acquisition
Special considerations related to:	
Sex and gender and sexual orientation	In the United States in 2022, 67% of the new HIV infections were among men who have sex with men, 2% were among transgender women, and < 1% each were among transgender men and gender nonbinary individuals.[22,23] In Latin America and Thailand, the HIV epidemic also disproportionately affects men who have sex with men and transgender women.[24-26] In South Africa, there is a generalized HIV epidemic, with disproportionately higher HIV incidence in men who have sex with men and transgender women.[27,28] In this trial, 22% of participants were transgender or gender nonbinary.
Race or ethnic group	In the United States in 2022, 70% of the new HIV infections were among Black/African American (37%) and Hispanic/Latine (33%) people, despite these groups accounting for only 12% and 18% of the United States population, respectively.[29] In this trial, 67% of participants were non-White and 63% were Hispanic or Latine.
Geography	The 1.3 million new global HIV infections in 2023 included 450,000 infections in Eastern and Southern Africa, 300,000 in Asia and the Pacific, 120,000 in Latin America, and 56,000 in Western and Central Europe and North America.[30] The trial population was enrolled from seven different countries: Brazil, United States (including Puerto Rico), Peru, Thailand, South Africa, Argentina, and Mexico.
Age	In the United States in 2022, 19% of HIV diagnoses were in people aged 13 to 24 years.[23] This trial

	included adolescents and 34% of participants were aged 16 to ≤ 25 years.
Overall representativeness of this trial	The participants in the present trial are representative of diverse global populations who have high likelihood of HIV acquisition and who have been historically underrepresented in clinical trials.

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