Supplementary Appendix

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

Supplementary Appendix

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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 PrEP agents, especially in women. Because F/TDF is effective for PrEP in women, placebo-controlled trials are not acceptable. Traditional non-inferiority trials are also infeasible in women because two out of three previously conducted placebo-controlled trials of F/TDF in women failed to demonstrate efficacy due to non-adherence[1,2]. This makes it infeasible to determine a noninferiority margin. Finally, superiority trials can be considered, but superiority may not be a reasonable expectation for all new PrEP agents, for instance F/TAF versus F/TDF in the present study. Therefore, working with a broad consortium of field experts from academia, regulatory agencies and pharmaceutical innovators, we developed and implemented the design presented here[3].

HIV diagnostic testing and case adjudication

Central laboratory testing was conducted by LabCorp, Inc. At the screening and Day 1 visits, HIV testing included a rapid, point-of-care, fourth-generation HIV-1/2 antibody/antigen test conducted at the site (Determine^{tm}, Abbott), an instrumented fourth-generation HIV-1/2 antibody/antigen test (Siemens) conducted at the central laboratory, and quantitative HIV RNA NAAT (Cobas 6800).

At subsequent study visits, HIV testing included a rapid fourth-generation HIV-1/2 antibody/antigen test conducted at the site and an instrumented fourth-generation HIV-1/2 antibody/antigen test conducted at the central laboratory.

In all cases, positive testing by central laboratory HIV-1/2 antibody/antigen test was confirmed with an HIV-1/2 antibody differentiation assay (Geenius™ HIV 1/2 Supplemental Assay). Discordant serological results were further tested by qualitative HIV RNA NAAT (Cobas Ampliprep-cobas TaqMan 2.0).

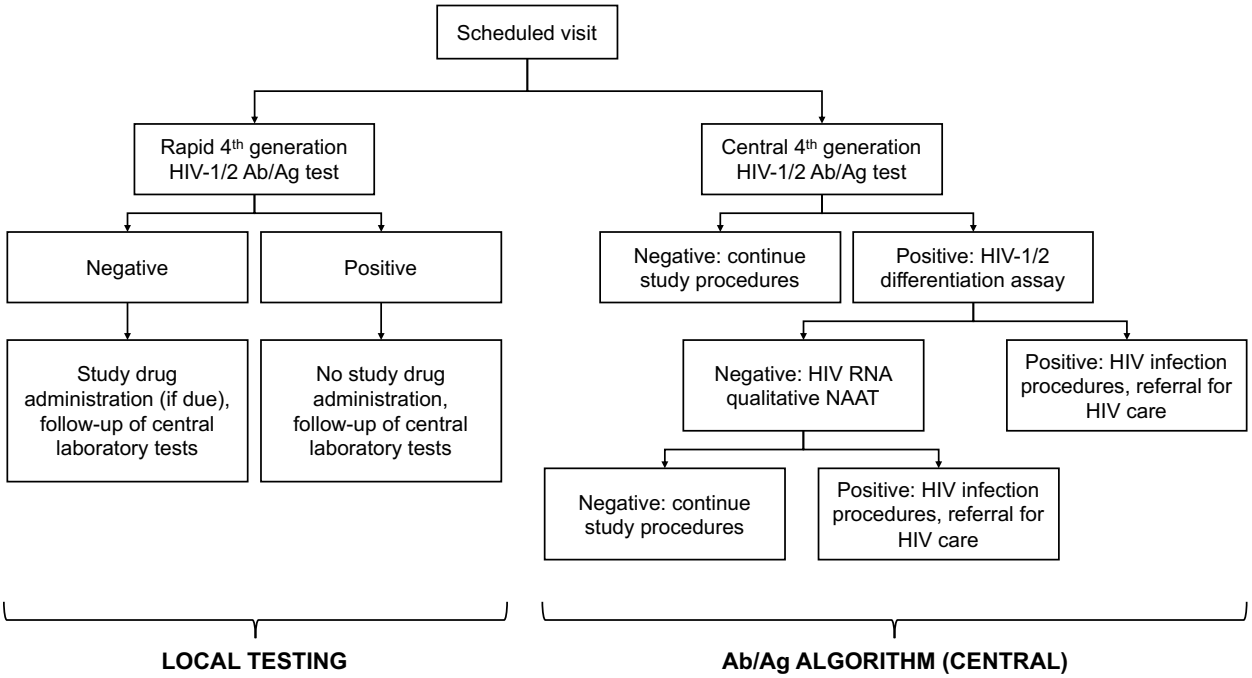
The HIV testing algorithm is depicted in Figure S1.

Retrospective quantitative HIV RNA NAAT testing was conducted using stored samples from the preceding study visit(s) for any participants diagnosed with incident HIV infection.

A blinded three-physician adjudication committee reviewed all positive post-screening HIV testing results. Members determined by majority vote whether HIV test results indicated HIV infection, a false-positive test result, or ambiguous results requiring additional testing. The committee then determined the date of diagnosis for HIV cases, defined as the earliest study day with evidence of HIV infection in a participant determined to have incident HIV infection, considering both prospective test results and retrospective RNA testing. HIV cases were considered incident if the date of diagnosis was after study day 1 (ie, at the time of randomization), or were considered baseline cases if the date of diagnosis was determined to be on study day 1. False positive results were observed in the study, as expected. Suspected false

positive results were assessed using quantitative RNA testing. Positive rapid HIV test results were considered false positive if the central laboratory fourth generation antibody/antigen test was negative and a contemporaneous quantitative HIV-1 RNA test was resulted as "none detected". Positive central laboratory fourth generation antibody/antigen test results were considered false positive if two consecutive quantitative HIV-1 RNA tests were resulted as "none detected" (one contemporaneous and one follow-up).

Figure S1: HIV- testing algorithm



Adapted from CDC HIV testing algorithm.[4-6] 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

Each site developed and implemented individualized adherence counseling, informed by national and global PrEP guidelines and adapted with approaches suitable for their specific setting and participant populations. Sites tailored adherence support approaches for their settings and to leveraged their prior experience in PrEP clinical trial conduct. Pill counts were performed at each visit and were used by sites to inform adherence counseling. Self-reported adherence data were also collected digitally as part of the study's protocol-defined questionnaires.

Excerpts from the PURPOSE 1 Full Statistical Analysis Plan

Planned Interim Analysis

An external independent multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform interim reviews of the data (both interim efficacy and periodic safety) in order to protect participant welfare and preserve study integrity. To ensure the best interests of the participants, the DMC will make recommendations to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

Interim Analyses of Safety Data

The first meeting of the DMC will be when the first 300 participants have completed their Week 8 visit to evaluate the safety of LEN. While enrollment will not be paused during this safety review, enrollment will not exceed 600 participants before the safety review is conducted and, if determined by the DMC, the study will be allowed to continue. Enrollment of adolescents (participants aged 16 and 17 years) will commence following the first DMC review of the safety data and recommendation to continue the study. Additional DMC review meetings of safety data will occur approximately annually thereafter during the Randomized Blinded Phase (RBP) of the study.

Interim Analyses of Efficacy Data

The DMC will formally evaluate efficacy and futility data, only once, after 50% of participants enrolled have completed Week 52 of the study or prematurely discontinued from the study. The DMC may recommend stopping the study early if the prespecified efficacy or futility evaluation criteria are met. If the RBP is stopped early due to an efficacy outcome, the interim analysis will serve as the primary analysis. The interim analyses results may be discussed with regulatory agencies to seek guidance for the overall clinical development program.

The DMC's role and responsibilities and the scope of analysis to be provided to the DMC are provided in a mutually agreed upon charter, which defines the DMC membership, meeting logistics, and meeting frequency.

Planned Primary Analysis

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. Analysis of the primary endpoint at this primary analysis will serve as the last alpha spending analysis to evaluate the HIV-1 incidences for the LEN and F/TAF study drug groups compared to the bHIV and F/TDF HIV-1 incidence.

Analysis Sets

All Screened Set

All Screened Set includes all participants who were screened for HIV-1 in the Incidence Phase and had non-missing HIV-1 diagnosis based on HIV test (defined as at least one non-missing central laboratory HIV test including the HIV-1/2 Ag/Ab screening, HIV-1/2 differentiation Ab, HIV-1/2 RNA qualitative or HIV-1 RNA quantitative test) at Incidence Screening. Any additional participants who took at least 1 dose of any study drug (but missing central laboratory HIV tests at Incidence Screening) will be included in the All Screened Set and considered as HIV-1 negative. This is the primary analysis set for estimating the bHIV.

All Randomized Analysis Set

All Randomized Analysis Set includes all participants who were randomized in the study.

Full Analysis Set (FAS)

The ideal evaluation of efficacy would follow ITT principles and based on an ITT analysis set. However, following ICH-E9 guidance, the term Full Analysis Set (FAS) is used to describe the analysis set which is as complete as possible and as close as possible to the ITT ideal that is suitable for a proper interpretation of efficacy data from a PrEP clinical trial.

The FAS includes all randomized participants who took at least 1 dose of any study drug and have not been diagnosed with HIV-1 on or prior to first dose date (as determined by the HIV Adjudication Committee confirming an HIV-1 infection diagnosis date on or prior to the first dose date of study drug). This is the primary analysis set for efficacy analyses for participants who entered the RBP of the study. Participants who have a negative rapid test at Day 1 are permitted to be dosed prior to receipt of the Day 1 central laboratory test results; however, participants who were diagnosed with HIV-1 based on central lab tests on or prior to first dose date will be excluded from the FAS.

Randomized Blinded Phase Safety Analysis Set

The RBP Safety Analysis Set includes all participants who took at least 1 dose of any study drug. This is the primary analysis set for RBP safety analyses.

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 here.

Multiple Alpha-Controlled Hypotheses

There are 8 alpha-controlled efficacy evaluations planned for this study and the null hypothesis for each one is listed in Table S1 below.

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

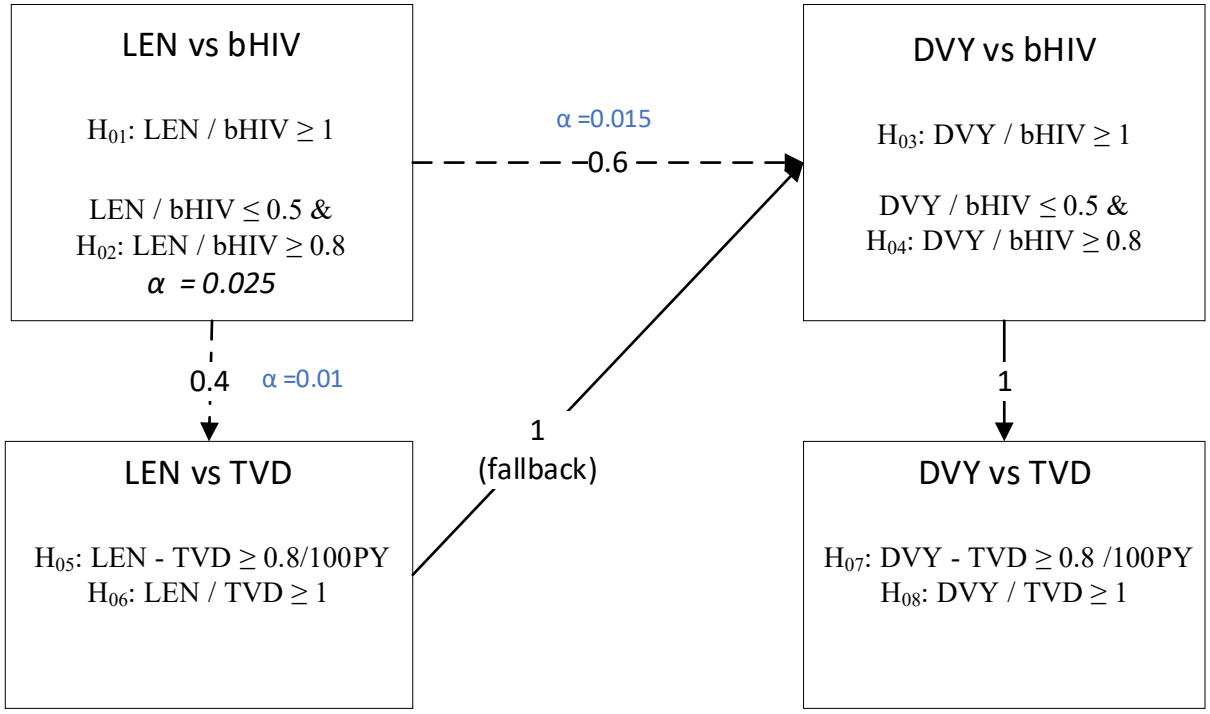
Table S1. Testing of Null Hypotheses

Objectives	Null Hypothesis	Interpretation from Rejecting Null Hypothesis
LEN Primary Objectives	H_{01}: LEN / bHIV ≥ 1	HIV-1 incidence in LEN is significantly lower than bHIV.
	H_{02}: LEN / bHIV ≥ 0.8	HIV-1 incidence in LEN is significantly and at least 20% lower than bHIV and the point estimate LEN/bHIV ≤ 0.5.
DVY Primary Objectives	H_{03}: DVY / bHIV ≥ 1	HIV-1 incidence in F/TAF is significantly lower than bHIV.
	H_{04}: DVY / bHIV ≥ 0.8	HIV-1 incidence in F/TAF is significantly and at least 20% lower than bHIV and the point estimate of DVY/bHIV ≤ 0.5.
LEN Secondary Objectives	H_{05}: LEN – TVD ≥ 0.8/100 PY	HIV-1 incidence in LEN is not substantially greater than F/TDF (LEN efficacy is comparable to F/TDF).
	H_{06}: LEN / TVD ≥ 1	HIV-1 incidence in LEN is significantly lower than F/TDF.
DVY Secondary Objectives	H_{07}: DVY – TVD ≥ 0.8/100 PY	HIV-1 incidence in F/TAF is not substantially greater than F/TDF (F/TAF efficacy is comparable to F/TDF).
	H_{08}: DVY / TVD ≥ 1	HIV-1 incidence in F/TAF is significantly lower than F/TDF.

PY: person-years

Gatekeeping (following the numbered null hypothesis sequence), alpha-splitting and fallback procedures will be used to control the Type I error rate. Figure S2 below depicts the overall testing procedure for multiple alpha-controlled endpoints/hypothesis testing of the efficacy evaluation.

Figure S2. Overall Testing Procedure



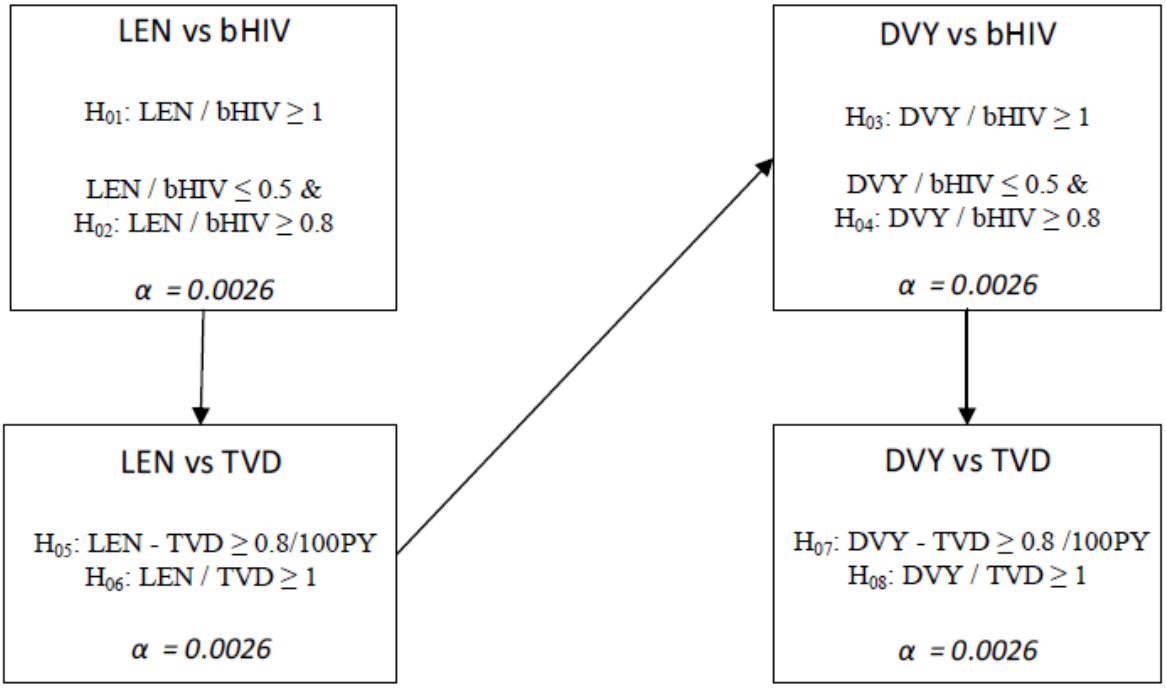
Note: Displayed alpha levels are the overall one-sided alpha (total alpha for both the interim and the primary analyses). Testing within each block is sequential. Transitional weights from one node to another indicates fraction of local significance level at the first node that is added to local significance level at the second node if the first node is rejected.

The overall alpha split will be between H_{03} (α = 0.015) and H_{05} (α = 0.01). The fallback procedure will be implemented for H_{03} if H_{06} is rejected; that is, 0.01 will be added to 0.015 for α = 0.025 to test H_{03} and the subsequent hypotheses within that block.

Alpha Splitting for Multiple Analyses (Interim and Primary Analyses)

The testing procedure at the interim analysis is shown in Figure S3. Considering that the FDA interim stopping criteria requires LEN superiority over bHIV (H_{01} and H_{02}) followed by LEN superiority over F/TDF (H_{05} and H_{06}), the overall testing procedure is revised for the interim efficacy analysis and a gated sequential testing approach is planned where the nominal alpha levels for the interim analysis are set at $\alpha_1 = 0.0026$.

Figure S3. Testing Procedure at the Interim Analysis

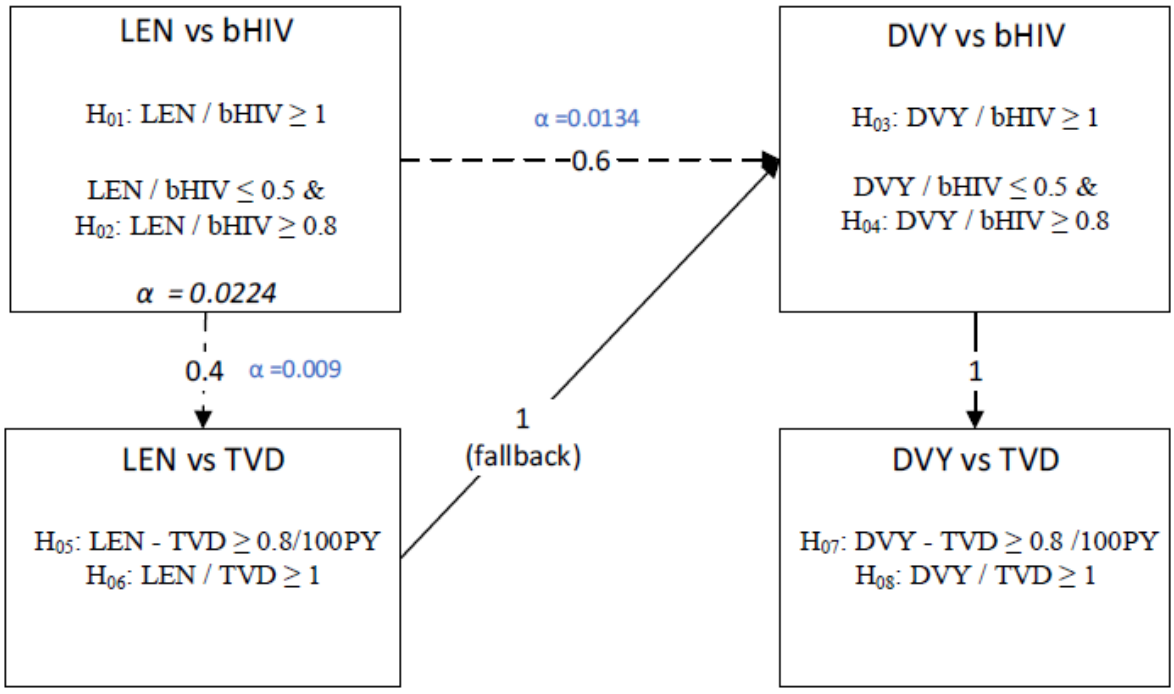


Note: Alpha levels are one-sided. Testing within each block is sequential.

At the interim analysis, given the FDA interim stopping criteria, the RBP of the trial will stop early if superiority of LEN over bHIV, designated H_{02} with the point estimate of $LEN/bHIV \leq 0.5$, and over F/TDF, designated H_{06}, 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. If the RBP of the trial is stopped early for efficacy, hypotheses H_{03}, H_{04}, H_{07}, H_{08} will be tested according to the scheme in Figure S3.

If the RBP continues to the primary analysis, the null hypotheses H_{01}, H_{02}, …, H_{08} will be tested according to the scheme in Figure S4, consistent with the overall testing procedure specified in Figure S2. Boundaries at the primary analysis will be based on the Bonferroni method, i.e., in Figure S5, the starting alpha is the difference between the overall alpha ($\alpha = 0.025$) and alpha spent at the interim ($\alpha_1 = 0.0026$). For example, the alpha for the "LEN vs bHIV" block is 0.025 – 0.0026 = 0.0224.

Figure S4. Testing Procedure at the Primary Analysis



Note: The one-sided α for the primary analysis is based on the Bonferroni method (primary alpha = 0.025 – interim alpha). Testing within each block is sequential. If H_{06} is rejected the fallback procedure will be implemented for H_{03} and the subsequent hypotheses. Transitional weights from one node to another indicates fraction of local significance level at the first node that is added to local significance level at the second node if the hypotheses in the first node are rejected.

The success criteria for LEN at the primary analysis are to demonstrate both superiority of-LEN versus bHIV, designated H_{02} with the point estimate of $LEN/bHIV \leq 0.5$, at $\alpha_2 = 0.0224$ and comparability of LEN to F/TDF, designated H_{05}, at $\alpha_2 = 0.009$.
The evaluation of F/TAF efficacy will also follow the procedures as prespecified in Figures S2, S3, and S4.
If adequate safety and efficacy of LEN is demonstrated, participants will be given the option to transition to the LEN open-label extension phase of the trial once the RBP is stopped.

Efficacy Analyses

The primary efficacy endpoint is the diagnosis of HIV-1 infection for the randomized phase and diagnosis of recent HIV-1 infection for the incidence phase of the study. The recent HIV-1 infection will be used to estimate the bHIV reported per 100 person-years (PY) computed based on the recent infection testing algorithm (RITA).

A high-level description of efficacy objectives and analyses is presented in Table S2 to frame the efficacy analysis plan detailed later.

Table S2. Summary for Key (Alpha-Controlled) Efficacy Evaluations

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

Definition of HIV-1 Infection (Incidence Phase)

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 Antibody/antigen 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.[7]

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 (ie, 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 HIV-1 incidence formula similar to Kassanjee et al.,[8] adjusting for participants with HIV-1 who may not have recency results (see Figure S5).

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

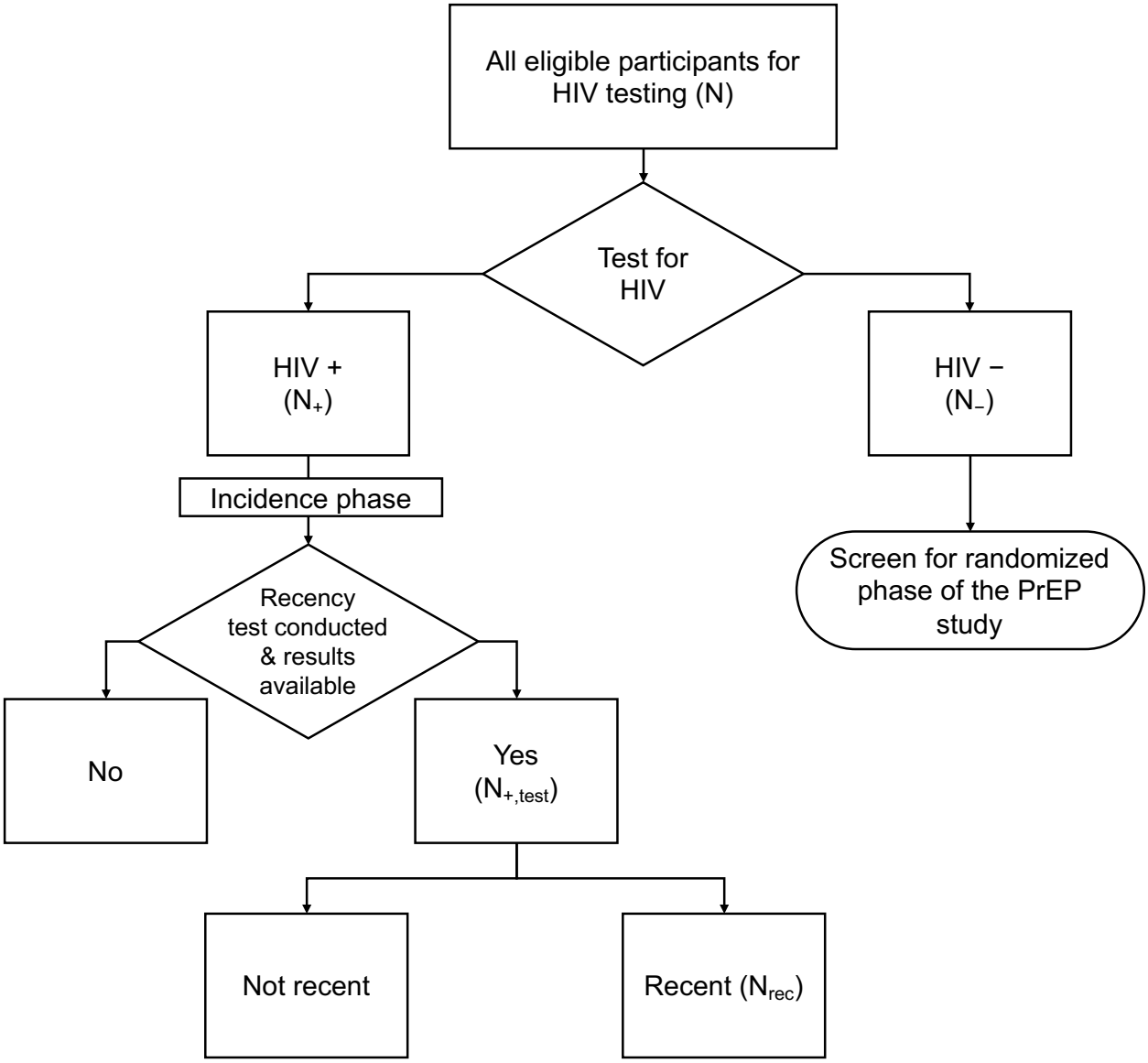
The variance of $\hat{\lambda}_0$ in the log scale $\hat{\sigma}^2_{\log(\hat{\lambda}_0)}$ will be estimated by the delta method, as provided by Gao et al.[9] (see below), considering the variance of Ω, β, and the observed counts of N_-, $N_{+,test}$, N_{rec}:

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

$$= + \frac{\sigma_\Omega^2}{(\Omega - \beta T)^2} + \sigma_\beta^2 \left[\frac{N_{+,test}\Omega - N_{rec}T}{(N_{rec} - N_{+,test}\beta)(\Omega - \beta T)}\right]^2$$

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.

Figure S5. Schema for the Estimation of bHIV Incidence



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

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.[10] 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 S3 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,[3] by Duong et al.,[11] the CDC 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.[10] 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 Lag-EIA 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 Figure S5 for details.

Table S3. 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.[10] will be used for bHIV estimation. Table S4 gives the assay parameters and their rSEs for $T = 2$ years (based on the RITA cutoffs in Table S3). The sample size calculation in the protocol was also based on Kassanjee et al.[10] with $T = 2$ years for pooled samples.

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, and infections from Uganda to be 56% subtype A, 41% subtype D, and 3% subtype C based on literature review.

Table S4. MDRI and FRR[10] (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]

a Based on the Sedia LAg-EIA and RITA cutoffs in Table S3 (ie, 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.

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 w_1, w_2 be the proportion of HIV-1 infections from South Africa and Uganda, respectively. The distribution of the three subtypes is:

1) Subtype A: $0.56w_2$
2) Subtype C: $w_1+0.03w_2$
3) Subtype D: $0.41w_2$

Let Ω_A, Ω_C, Ω_D be the MDRI for the subtypes A/C/D, and $\sigma_{\Omega,A}$, $\sigma_{\Omega,C}$, $\sigma_{\Omega,D}$ be the corresponding standard errors, which will be computed as the product of MDRI and the rSE of the MDRI in Table S4. The overall MDRI will be estimated by

$$\Omega = 0.56w_2\Omega_A + (w_1 + 0.03w_2)\Omega_C + 0.41w_2\Omega_D.$$

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

$$\sigma_\Omega = \sqrt{(0.56w_2)^2\sigma_{\Omega,A}^2 + (w_1 + 0.03w_2)^2\sigma_{\Omega,C}^2 + (0.41w_2)^2\sigma_{\Omega,D}^2}.$$

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_A, β_C, and β_D be the FRR for the subtypes A/C/D, and $\sigma_{\beta,A}$, $\sigma_{\beta,C}$, and $\sigma_{\beta,D}$ be the corresponding standard errors, which will be computed as the product of the FRR and the rSE of the FRR in Table S4. The overall FRR will be estimated by

$$\beta = 0.56w_2\beta_A + (w_1 + 0.03w_2)\beta_C + 0.41w_2\beta_D.$$

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

$$\sigma_\beta = \sqrt{(0.56w_2)^2\sigma_{\beta,A}^2 + (w_1 + 0.03w_2)^2\sigma_{\beta,C}^2 + (0.41w_2)^2\sigma_{\beta,D}^2}.$$

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[10,3] 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 S4 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 LEN, F/TAF, and F/TDF study drug groups while at-risk of HIV-1 infection in study.

The HIV-1 incidence in LEN, F/TAF, 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 stop taking any PrEP during the study].
The exact $(1-\alpha)\times 100\%$ CI for λ_1 will be constructed as follows[12]:

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

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.[9]

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

Duration of at-risk of HIV-1 infection in study is defined as the time after Day 1 (first dose date) through the last at-risk of HIV-1 infection date in 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 PY) and as the number and percentage of participants at risk of HIV-1 infection in study for specified periods, ie, ≥ 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 LEN SC injection was put on clinical hold, pausing the screening and enrollment of new participants and continued dosing of injectable LEN 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 LEN SC or placebo injections every 6 months) according to their original randomized study drug assignment after Protocol Amendment 2. As the clinical hold occurred very early in the study, there were only 195

participants and 89.4 person-years affected. Notably, no HIV infections occurred during the clinical hold period.

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 ignored (ie, a treatment policy strategy) for the primary efficacy evaluations, meaning that the affected person time and any events occurring therein are included in the analysis.

Efficacy Evaluations for Key (Alpha-Controlled) Statistical Hypotheses

Eight alpha-controlled statistical hypotheses tests are planned for this study and the null hypothesis for each one is listed in Table S1. The testing procedures and methods to control the alpha is also presented above

Primary Efficacy Evaluations (Comparison with bHIV)

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

Null hypothesis: H_{01}: LEN/bHIV ≥ 1.0

Alternative hypothesis: LEN/bHIV < 1.0

It will be concluded that HIV-1 incidence in the LEN 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 is defined as the HIV-1 incidence rate ratio of at least 20% reduction in the LEN 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_{05}.

Similarly, for the F/TAF study drug group, the corresponding statistical hypotheses are the primary analysis of H_{03}: DVY/bHIV ≥ 1.0 (superiority over bHIV) and for the primary analysis the success criteria for the US FDA regulatory review of H_{04}: DVY/bHIV ≥ 0.8 (at least 20% reduction compared with the bHIV) with a point estimate of DVY/bHIV ≤ 0.5 and comparability to F/TDF formulated as the key alpha-controlled H_{07}. The alpha allocated for H_{04} and H_{07} follow the alpha control rules specified in Figure S2.

Methods for the Primary Efficacy Evaluations

The incidence rate ratio of the LEN (or F/TAF) 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.[9] (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[9]:

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

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 LEN (or F/TAF) 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 and Gao.[13]

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 LEN relative to F/TDF, that is, null hypothesis H_{05}. Rejection of this hypothesis will support a conclusion that the HIV-1 incidence in the LEN 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.[14] with an additional modification to use the exact CI for the single Poisson rate parameter instead of the approximate CI recommended by Li et al.

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:[12]

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

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) 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 LEN 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[13] 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 $U(\alpha) = 0.8/100$ PY for α, then $\alpha/2$ will be the 1-sided p-value.

The hypothesis H_{07} (comparability of F/TAF and F/TDF) will be evaluated similarly.

Analysis Methods for Ratio of HIV-1 Incidence Rates

Ratio of HIV-1 incidence rates will evaluate the relative statistical difference between LEN (or F/TAF) and F/TDF. The rate ratios of HIV-1 incidence between LEN and F/TDF and between F/TAF 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/TAF) 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_{06} and H_{08} will only be tested sequentially after H_{05} and H_{07} have been rejected, respectively (Figures S3 and S4).

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 LEN over bHIV, designated H_{02} with the point estimate of $LEN/bHIV \leq 0.5$, and over F/TDF, designated H_{06}, 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.
If the RBP of the trial is stopped early for efficacy, hypotheses H_{03}, H_{04}, H_{07}, H_{08} will be tested according to the scheme in Figure S4.

Futility Boundary

The study will be stopped if F/TDF is found to be superior to both LEN and F/TAF or F/TAF is found to be superior to LEN at $\alpha_1 = 0.0026$. The comparison between LEN and F/TAF will be similar to the comparison between LEN and F/TDF, except to change the F/TDF arm to F/TAF arm. Additionally, as both LEN and F/TAF are under study, the trial continuation or early stopping for futility will be evaluated if either of the two following situations occurs:

- If F/TDF is found to be superior to F/TAF (rate ratio) at level $\alpha_1 = 0.0026$, this would lead to stopping (and unblinding) the F/TAF arm. In this case, the blinded trial may continue with LEN and F/TDF arms.

- If either F/TDF or F/TAF is found to be superior to LEN (rate ratio) at level $\alpha_1 = 0.0026$, this would lead to stopping (and unblinding) the LEN arm. In this case, the study would be unblinded and may continue as an open-label study.

Evaluation of Adherence in F/TAF and F/TDF 10% Cohort

Adherence was objectively assessed by measuring tenofovir diphosphate concentrations in dried blood spots in a pre-selected, representative, random 10% subgroup of the F/TAF and F/TDF groups. The methodology and establishment of the adherence thresholds has been described elsewhere[15-17]. Adherence thresholds are noted below. Due to the differences in circulating plasma tenofovir concentrations, which are 90% lower with TAF vs. TDF, the dried blood spot methodology analyzes a different amount of dried blood for each drug: one 3 mm punch from the DBS storage card is analyzed for participants on F/TDF and two 7 mm punches are analyzed for participants on F/TAF. Considering the difference in plasma drug concentrations and sampling methodology, drug concentration cutoffs for the high/medium/low adherence strata have been determined separately for TDF and TAF, using data from directly observed dosing cohorts receiving with TDF or TAF. Applying the drug concentration thresholds specific for the individual drugs allows for direct comparisons in adherence between F/TAF and F/TDF groups.

Table S5. Adherence Level Definitions Based on DBS Concentration

	Adherence Level (Daily Tablets/Week)		
	Low (<2)	**Medium (2-3)**	**High (≥4)**
F/TDF (fmol/Punch)	< 350	350 to < 700	≥ 700
F/TAF (fmol/Punches)	< 450	450 to < 900	≥ 900

Case-Control Substudy

Conditional logistic regression model will be used to estimate the odds ratio (and its 95% confidence interval) assessing the association between HIV infection status and the adherence levels based on DBS concentration at HIV diagnosis for cases and controls. The 3 ordinal adherence categories will be dichotomized to estimate the odds of HIV infection when adherence is low compared to when adherence is not low (medium or high adherence).

The matched case-control substudy, control participants will be matched to cases on a (up to based on availability) 5:1 ratio based on the following criterion order

1) Study drug group

2) Time of HIV-1 diagnosis, where time is defined as the visit that an HIV-1 case was first considered to be HIV-1 positive based on laboratory data and HIV Adjudication Committee determination.

3) Risk behavior: Baseline Risk as assessed by the VOICE Score: Controls with VOICE score ≥ Case Voice Score will be selected.

4) Location: As the number of participants from each site varies, the matching location will be selected based on widening the geographic area in the following order to achieve the total number of controls

   a) Investigational site (enrolled by the same investigator)

Control participants will be selected randomly if the available number of control participants meeting the above criteria exceeds 5 in a site.

The analysis will be within each study drug group and will include DBS drug concentration levels, at the time of infection as the primary predictor. If a control participant has DBS collected at more than one visit within a window, then the record with DBS collection study day closest to the diagnosis study day of the case participant will be selected and if they are equally apart from the diagnosis study day of the case participant (one before and one after) then the one after the study day of the case participant will be selected.

DBS cards at the time of diagnosis may not have been collected for HIV diagnosed participants or the sample may not meet specifications and be rejected by the analytical laboratory. In general, missing DBS concentration at the time of HIV-1 diagnosis will be imputed by considering:

1) the last known TFV-DP concentration (C) prior to diagnosis

2) days between the last dose date and HIV-1 diagnosis (HIV-1 diagnosis date – last dose date) where any negative days (last dose is after HIV-1 Dx) are set to 0

3) days between the last TFV-DP concentration (C) prior to diagnosis and HIV-1 diagnosis (HIV-1 diagnosis date – last DBS date)

4) the decay rate, k, of TFV-DP concentration in RBC calculated based on half-life, $t_{1/2}$, of each study drug group, where $k=0.693/t_{1/2}$.

The imputed concentration, $C_i = C \times e^{-k \times t}$, where t is the min of 2) and 3) above.

TFV-DP has shown the median (range) half-life of 17 (14 to 23) days for F/TDF in previous DOT studies of F/TDF [17] and mean (95% CI) 20.8 days (19.3 to 21.3) for F/TAF [16].

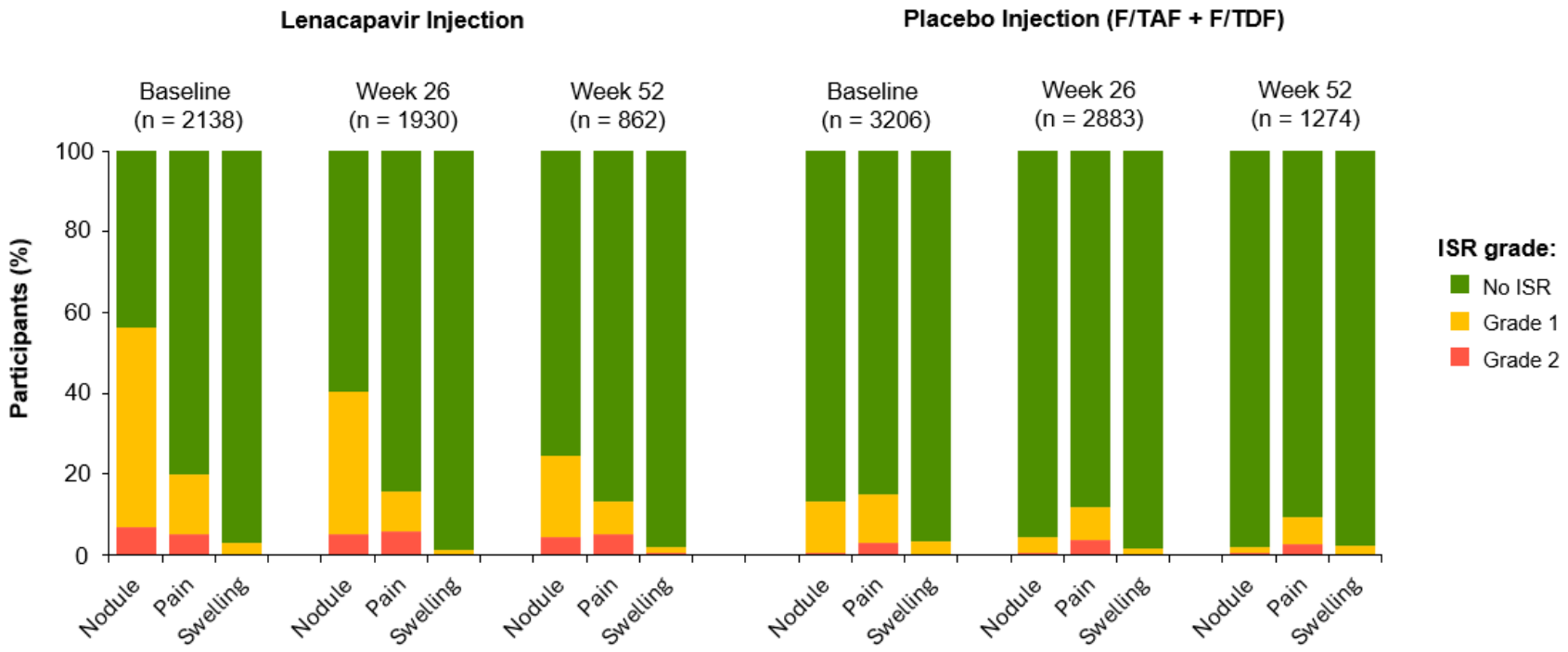
Safety analyses

All safety data from both phases of the study will be included in data listings. The RBP safety analyses will include any safety data during the temporary interruptions in the study drug administration in summaries under the randomized study drug group (eg safety data collected while any SC LEN randomized participants received open label F/TDF due to the clinical hold are summarized under SC LEN study drug group). Temporary interruption to RBP study drug includes the clinical hold period during which participants may receive temporary oral study

drug (open label F/TDF or open-label F/TAF or blinded weekly oral LEN/PTM bridging) as well as blinded weekly oral LEN/PTM bridging following late SC injections outside of clinical hold.

Supplementary Results

Figure S6: Injection Site Reactions (nodules, pain, and swelling)



Subcutaneous nodules, injection site pain, and swelling were the most commonly reported injection site reactions; over the period of study they occurred in 63.8%, 31.2%, and 4.4% of participants in the lenacapavir group, respectively, versus 16.6%, 23.7%, and 5.4% of participants given placebo injections. Grade 1 and 2 injection site reactions are shown; there was a single case of grade 3 injection site nodule (associated with Week 52/third injection) and one of injection site pain (associated with Week 26/second injection) in the lenacapavir group.

Table S6. HIV Test Results for Participants Adjudicated to Have HIV at Baseline.

Case	Group	Week	Rapid Antibody/antigen	Central Antibody/antigen	Ab differentiation	Viral load (copies/mL)
1	LEN	Baseline	negative	positive	negative	4,540,000
		Day 8	positive	ND	ND	26,500
		Day 29	ND	ND	ND	195
		Day 91	ND	ND	ND	<20
2	LEN	Baseline	negative	positive	negative	105,000,000
		Day 9	negative	positive	positive	227,000
3	LEN	Baseline	negative	positive	negative	80,500,000
		Day 29	positive	ND	ND	ND
		Day 75	ND	positive	positive	ND
4	LEN	Baseline	negative	negative	ND	129,000
		Day 15	ND	ND	ND	269,000
		Day 29	ND	ND	ND	353
		Day 95	ND	ND	ND	none detected
5	F/TAF	Baseline	negative	positive	negative	36,200,000
		Day 9	ND	ND	ND	191,000
		Day 41	ND	ND	ND	22,900
6	F/TDF	Baseline	negative	negative	ND	47,500
		Day 7	negative	negative	ND	59,000
		Day 13	positive	positive	positive	187,000

Case	Group	Week	Rapid Antibody/antigen	Central Antibody/antigen	Ab differentiation	Viral load (copies/mL)
		Day 49	ND	ND	ND	67,100
		Day 96	ND	ND	ND	37,600
7	F/TDF	Baseline	negative	positive	negative	512,000
		Day 15	ND	ND	ND	1,130
		Day 43	ND	positive	positive	62
		Day 49	ND	ND	ND	43
		Day 100	ND	ND	ND	none detected

All results through 100 days of follow-up are presented. ND, not done

Table S7. Baseline Demographics and Clinical Characteristics

	All Screened Set	HIV Diagnosis at Incidence Screening		Randomized	
	(N=8094)	Yes (N=504)	No (N=7590)	Yes (N=5368)	No (N=2222)
Age (Years)					
N	8094	504	7590	5368	2222
Mean (SD)	21 (2.2)	22 (2.1)	21 (2.2)	21 (2.1)	22 (2.2)
Median	21	23	21	21	22
Q1, Q3	20, 23	21, 24	20, 23	19, 23	20, 24
Min, Max	16, 26	17, 25	16, 26	16, 26	16, 26
Age Categories (Years)					
16 to <18	154 (1.9%)	3 (0.6%)	151 (2.0%)	125 (2.3%)	26 (1.2%)
>= 18	7940 (98.1%)	501 (99.4%)	7439 (98.0%)	5243 (97.7%)	2196 (98.8%)
Race*					
Black*	8085 (99.9%)	503 (99.8%)	7582 (99.9%)	5362 (99.9%)	2220 (99.9%)
Ethnicity					
Not Hispanic or Latino	8094 (100.0%)	504 (100.0%)	7590 (100.0%)	5368 (100.0%)	2222 (100.0%)
Screening Weight (kg)					
N	6751	20	6731	5368	1363
Mean (SD)	67.2 (17.50)	65.1 (15.57)	67.2 (17.50)	67.7 (17.76)	65.6 (16.35)
Median	63.1	67.3	63.1	63.4	62
Q1, Q3	54.7, 76.1	52.6, 75.3	54.7, 76.1	54.8, 76.9	53.9, 73.3
Min, Max	36.5, 192.1	41.0, 100.4	36.5, 192.1	36.5, 192.1	37.8, 142.8

	All Screened Set	HIV Diagnosis at Incidence Screening		Randomized	
Screening Height (cm)					
N	6748	19	6729	5368	1361
Mean (SD)	158.8 (6.37)	160.2 (7.77)	158.8 (6.37)	158.7 (6.43)	159.0 (6.12)
Median	159	160	159	159	159
Q1, Q3	155.0, 163.0	153.0, 165.0	155.0, 163.0	155.0, 163.0	155.0, 163.0
Min, Max	110.0, 189.0	148.7, 178.0	110.0, 189.0	110.0, 189.0	128.0, 181.0
Screening Body Mass Index (kg/m^2)					
N	6748	19	6729	5368	1361
Mean (SD)	26.6 (6.56)	25.3 (6.45)	26.6 (6.56)	26.8 (6.65)	25.9 (6.16)
Median	25.1	26.1	25.1	25.2	24.4
Q1, Q3	21.8, 30.1	19.6, 29.1	21.8, 30.1	21.9, 30.4	21.4, 29.1
Min, Max	14.6, 62.7	16.0, 42.9	14.6, 62.7	14.6, 62.7	15.8, 53.7
Screening Waist Circumference (cm)					
N	6751	20	6731	5368	1363
Mean (SD)	82.8 (13.74)	80.1 (12.38)	82.8 (13.74)	82.9 (13.88)	82.2 (13.15)
Median	80	78.5	80	80	80
Q1, Q3	73.0, 90.0	71.5, 85.7	73.0, 90.0	73.0, 91.0	73.0, 89.0
Min, Max	41.0, 164.0	60.0, 105.0	41.0, 164.0	41.0, 164.0	59.0, 158.0
Highest Education Level					
Did not attend Primary School	92 (1.2%)	22 (6.8%)	70 (1.0%)	40 (0.7%)	30 (1.8%)
Some Primary School Education	779 (10.5%)	105 (32.6%)	674 (9.5%)	399 (7.4%)	275 (16.1%)
Primary School Complete	262 (3.5%)	26 (8.1%)	236 (3.3%)	168 (3.1%)	68 (4.0%)

	All Screened Set	HIV Diagnosis at Incidence Screening		Randomized	
Some Secondary School Education	3100 (41.9%)	108 (33.5%)	2992 (42.3%)	2297 (42.8%)	695 (40.6%)
Secondary School Degree Complete	2516 (34.0%)	57 (17.7%)	2459 (34.8%)	1964 (36.6%)	495 (28.9%)
Some College or University Degree	647 (8.7%)	4 (1.2%)	643 (9.1%)	494 (9.2%)	149 (8.7%)
- Missing -	698	182	516	6	510
Needs Help with Completion of Electronic Questionnaire					
Yes	4137 (55.9%)	265 (81.5%)	3872 (54.7%)	2757 (51.4%)	1115 (65.1%)
No	3261 (44.1%)	60 (18.5%)	3201 (45.3%)	2604 (48.6%)	597 (34.9%)
- Missing -	696	179	517	7	510
Current Marital Status					
Never Married	7042 (95.2%)	279 (86.6%)	6763 (95.6%)	5196 (96.9%)	1567 (91.5%)
Married (monogamous)	115 (1.6%)	10 (3.1%)	105 (1.5%)	52 (1.0%)	53 (3.1%)
Married (polygamous)	56 (0.8%)	5 (1.6%)	51 (0.7%)	21 (0.4%)	30 (1.8%)
Separated	177 (2.4%)	27 (8.4%)	150 (2.1%)	89 (1.7%)	61 (3.6%)
Divorced	4 (<0.1%)	1 (0.3%)	3 (<0.1%)	2 (<0.1%)	1 (<0.1%)
Widowed	2 (<0.1%)	0	2 (<0.1%)	2 (<0.1%)	
- Missing	698	182	516	6	510
Currently Living with Husband/Partner					
Yes	566 (7.7%)	40 (12.4%)	526 (7.4%)	354 (6.6%)	172 (10.0%)
No	6323 (85.5%)	226 (70.2%)	6097 (86.2%)	4733 (88.3%)	1364 (79.7%)
No Partner	506 (6.8%)	56 (17.4%)	450 (6.4%)	274 (5.1%)	176 (10.3%)
Prefer Not to Answer	1	0	1	1	0

	All Screened Set	HIV Diagnosis at Incidence Screening		Randomized	
- Missing	698	182	516	6	510
Husband/Partner Provide Financial and/or Material Support					
Yes	4539 (61.7%)	162 (50.3%)	4377 (62.2%)	3341 (62.7%)	1036 (60.9%)
No	2299 (31.3%)	103 (32.0%)	2196 (31.2%)	1710 (32.1%)	486 (28.6%)
No Partner	516 (7.0%)	57 (17.7%)	459 (6.5%)	280 (5.3%)	179 (10.5%)
Prefer Not to Answer	42	0	42	31	11
- Missing -	698	182	516	6	510
Husband/Partner Have Sex with Other Partners					
Yes	2166 (29.8%)	139 (43.2%)	2027 (29.1%)	1450 (27.5%)	577 (34.1%)
No	1625 (22.3%)	13 (4.0%)	1612 (23.2%)	1311 (24.9%)	301 (17.8%)
No Partner	519 (7.1%)	57 (17.7%)	462 (6.6%)	277 (5.3%)	185 (10.9%)
Unknown	2969 (40.8%)	113 (35.1%)	2856 (41.1%)	2226 (42.3%)	630 (37.2%)
Prefer Not to Answer	117	0	117	98	19
- Missing -	698	182	516	6	510
Frequency of Alcohol Use in the Past 3 Months					
Never	1782 (24.2%)	109 (34.0%)	1673 (23.7%)	1240 (23.2%)	433 (25.4%)
Monthly or less	2398 (32.6%)	57 (17.8%)	2341 (33.2%)	1835 (34.3%)	506 (29.7%)
2 to 4 times a month	2049 (27.8%)	76 (23.7%)	1973 (28.0%)	1547 (29.0%)	426 (25.0%)
2 to 3 times a week	642 (8.7%)	44 (13.7%)	598 (8.5%)	411 (7.7%)	187 (11.0%)
4 or more times a week	496 (6.7%)	35 (10.9%)	461 (6.5%)	310 (5.8%)	151 (8.9%)
Prefer Not to Answer	28	1	27	18	9
- Missing -	699	182	517	7	510

* All participants not listed as Black were multiracial

Table S8: Retention Based on Attending Study Visit and Receiving HIV Testing

	Lenacapavir		F/TAF		F/TDF		Total	
	Expected	**Actual (%)**	**Expected**	**Actual (%)**	**Expected**	**Actual (%)**	**Expected**	**Actual (%)**
Baseline	2138	2138 (100)	2137	2137 (100)	1070	1070 (100)	5345	5345 (100)
Week 4	2122	2086 (98.3)	2119	2081 (98.2)	1056	1029 (97.4)	5297	5196 (98.1)
Week 8	2107	2065 (98)	2107	2056 (97.6)	1050	1024 (97.5)	5264	5145 (97.7)
Week 13	2087	2057 (98.6)	2088	2044 (97.9)	1039	1022 (98.4)	5214	5123 (98.3)
Week 26	2007	1940 (96.7)	2014	1952 (96.9)	999	963 (96.4)	5020	4855 (96.7)
Week 39	1930	1815 (94)	1939	1824 (94.1)	955	895 (93.7)	4824	4534 (94)
Week 52	1051	985 (93.7)	1041	973 (93.5)	520	481 (92.5)	2612	2439 (93.4)
Week 65	417	379 (90.9)	431	395 (91.6)	203	179 (88.2)	1051	953 (90.7)
Week 78	165	145 (87.9)	176	163 (92.6)	81	74 (91.4)	422	382 (90.5)
Week 91	51	43 (84.3)	59	52 (88.1)	26	18 (69.2)	136	113 (83.1)
Week 104	19	18 (94.7)	16	15 (93.8)	8	6 (75)	43	39 (90.7)
Week 117	18	16 (88.9)	15	14 (93.3)	7	5 (71.4)	40	35 (87.5)
Week 130	9	1 (11.1)	6	0 (0)	3	0 (0)	18	1 (5.6)

Table S9: Incidence of Sexually Transmitted Infections Diagnosed Through Laboratory Tests Every 26 Weeks

	Number of STI Events/Person-years of Follow-Up (Incidence Rate per 100 Person-years)			
	Lenacapavir (N=2008)	**F/TAF (N=1999)**	**F/TDF (N=989)**	**Total (N=4996)**
Gonorrhea, Chlamydia or Trichomonas Vaginalis	930/1908.8 (48.7)	965/1899.4 (50.8)	452/933.4 (48.4)	2347/4741.6 (49.5)
Gonorrhea	207/1908.8 (10.8)	235/1899.4 (12.4)	101/933.4 (10.8)	543/4741.6 (11.5)
Chlamydia	537/1908.8 (28.1)	527/1899.4 (27.7)	246/933.4 (26.4)	1310/4741.6 (27.6)
Trichomonas Vaginalis	186/1908.0 (9.7)	203/1899.4 (10.7)	105/933.4 (11.2)	494/4740.8 (10.4)

Table S10: Grade 3 or Higher Treatment-Emergent Adverse Events

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
Number (%) of Participants with Any Grade 3 or Higher Treatment-Emergent Adverse Events (Excluding ISRs)	88 (4.1)	95 (4.4)	50 (4.7)
Number (%) of Participants with Any Grade 3 or Higher Treatment-Emergent Adverse Events (Including ISRs)	92 (4.3%)	97 (4.5%)	52 (4.9%)
Grade 3 (Severe)	79 (3.7%)	79 (3.7%)	46 (4.3%)
Grade 4 (Life-Threatening)	13 (0.6%)	12 (0.6%)	6 (0.6%)
Grade 5 (Death)	0	6 (0.3%)	0
Blood and lymphatic system disorders	7 (0.3%)	4 (0.2%)	4 (0.4%)
Grade 3 (Severe)	6 (0.3%)	3 (0.1%)	4 (0.4%)
Grade 4 (Life-Threatening)	1 (<0.1%)	1 (<0.1%)	0
Anaemia	2 (<0.1%)	4 (0.2%)	2 (0.2%)
Grade 3 (Severe)	2 (<0.1%)	3 (0.1%)	2 (0.2%)
Grade 4 (Life-Threatening)	0	1 (<0.1%)	0
Hypochromic anaemia	3 (0.1%)	0	0
Grade 3 (Severe)	2 (<0.1%)	0	0
Grade 4 (Life-Threatening)	1 (<0.1%)	0	0
Neutropenia	2 (<0.1%)	0	0
Grade 3 (Severe)	2 (<0.1%)	0	0
Anaemia of pregnancy	0	0	1 (<0.1%)
Grade 3 (Severe)	0	0	1 (<0.1%)
Lymphopenia	0	0	1 (<0.1%)
Grade 3 (Severe)	0	0	1 (<0.1%)

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
Cardiac disorders	0	2 (<0.1%)	0
Grade 4 (Life-Threatening)	0	1 (<0.1%)	0
Grade 5 (Death)	0	1 (<0.1%)	0
Ischaemic cardiomyopathy	0	1 (<0.1%)	0
Grade 5 (Death)	0	1 (<0.1%)	0
Nonreassuring foetal heart rate pattern	0	1 (<0.1%)	0
Grade 4 (Life-Threatening)	0	1 (<0.1%)	0
Eye disorders	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Cataract	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Gastrointestinal disorders	2 (<0.1%)	3 (0.1%)	3 (0.3%)
Grade 3 (Severe)	2 (<0.1%)	2 (<0.1%)	3 (0.3%)
Grade 4 (Life-Threatening)	0	1 (<0.1%)	0
Gastritis	1 (<0.1%)	0	2 (0.2%)
Grade 3 (Severe)	1 (<0.1%)	0	2 (0.2%)
Peptic ulcer	1 (<0.1%)	2 (<0.1%)	0
Grade 3 (Severe)	1 (<0.1%)	2 (<0.1%)	0
Abdominal pain lower	0	0	1 (<0.1%)
Grade 3 (Severe)	0	0	1 (<0.1%)
Haematemesis	0	1 (<0.1%)	0
Grade 4 (Life-Threatening)	0	1 (<0.1%)	0

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
General disorders and administration site conditions	4 (0.2%)	3 (0.1%)	2 (0.2%)
Grade 3 (Severe)	4 (0.2%)	3 (0.1%)	2 (0.2%)
Injection site ulcer	3 (0.1%)	2 (<0.1%)	1 (<0.1%)
Grade 3 (Severe)	3 (0.1%)	2 (<0.1%)	1 (<0.1%)
Fatigue	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Injection site nodule	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Injection site pain	0	0	1 (<0.1%)
Grade 3 (Severe)	0	0	1 (<0.1%)
Hepatobiliary disorders	0	2 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Grade 4 (Life-Threatening)	0	1 (<0.1%)	0
Cholelithiasis	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Hypertransaminasaemia	0	1 (<0.1%)	0
Grade 4 (Life-Threatening)	0	1 (<0.1%)	0
Immune system disorders	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Hypersensitivity	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Infections and infestations	18 (0.8%)	22 (1.0%)	8 (0.7%)

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
Grade 3 (Severe)	16 (0.7%)	21 (1.0%)	8 (0.7%)
Grade 4 (Life-Threatening)	2 (<0.1%)	1 (<0.1%)	0
Malaria	8 (0.4%)	7 (0.3%)	2 (0.2%)
Grade 3 (Severe)	8 (0.4%)	7 (0.3%)	2 (0.2%)
Urinary tract infection	1 (<0.1%)	3 (0.1%)	2 (0.2%)
Grade 3 (Severe)	1 (<0.1%)	3 (0.1%)	2 (0.2%)
Injection site abscess	0	4 (0.2%)	0
Grade 3 (Severe)	0	4 (0.2%)	0
Appendicitis	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Grade 3 (Severe)	0	1 (<0.1%)	1 (<0.1%)
Grade 4 (Life-Threatening)	1 (<0.1%)	0	0
Typhoid fever	0	2 (<0.1%)	1 (<0.1%)
Grade 3 (Severe)	0	2 (<0.1%)	1 (<0.1%)
Hepatitis A	0	1 (<0.1%)	1 (<0.1%)
Grade 3 (Severe)	0	1 (<0.1%)	1 (<0.1%)
Subcutaneous abscess	2 (<0.1%)	0	0
Grade 3 (Severe)	2 (<0.1%)	0	0
Brain empyema	1 (<0.1%)	0	0
Grade 4 (Life-Threatening)	1 (<0.1%)	0	0
Bronchitis	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Gastroenteritis	1 (<0.1%)	0	0

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
Grade 3 (Severe)	1 (<0.1%)	0	0
Helicobacter infection	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Lower respiratory tract infection	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Pelvic inflammatory disease	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Peritonitis	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Pneumonia	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Postoperative wound infection	0	1 (<0.1%)	0
Grade 4 (Life-Threatening)	0	1 (<0.1%)	0
Pyelonephritis	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Pyelonephritis acute	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Salpingitis	0	0	1 (<0.1%)
Grade 3 (Severe)	0	0	1 (<0.1%)
Sepsis	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Sinusitis	1 (<0.1%)	0	0

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
Grade 4 (Life-Threatening)	1 (<0.1%)	0	0
Tonsillitis	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Upper respiratory tract infection	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Injury, poisoning and procedural complications	11 (0.5%)	13 (0.6%)	5 (0.5%)
Grade 3 (Severe)	11 (0.5%)	9 (0.4%)	4 (0.4%)
Grade 4 (Life-Threatening)	0	1 (<0.1%)	1 (<0.1%)
Grade 5 (Death)	0	3 (0.1%)	0
Overdose	3 (0.1%)	1 (<0.1%)	0
Grade 3 (Severe)	3 (0.1%)	1 (<0.1%)	0
Road traffic accident	2 (<0.1%)	2 (<0.1%)	0
Grade 3 (Severe)	2 (<0.1%)	1 (<0.1%)	0
Grade 5 (Death)	0	1 (<0.1%)	0
Ankle fracture	2 (<0.1%)	0	0
Grade 3 (Severe)	2 (<0.1%)	0	0
Humerus fracture	0	0	2 (0.2%)
Grade 3 (Severe)	0	0	2 (0.2%)
Lower limb fracture	0	0	2 (0.2%)
Grade 3 (Severe)	0	0	2 (0.2%)
Stab wound	0	2 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Grade 5 (Death)	0	1 (<0.1%)	0

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
Thermal burn	1 (<0.1%)	1 (<0.1%)	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Grade 5 (Death)	0	1 (<0.1%)	0
Anaemia postoperative	0	0	1 (<0.1%)
Grade 4 (Life-Threatening)	0	0	1 (<0.1%)
Animal bite	0	0	1 (<0.1%)
Grade 3 (Severe)	0	0	1 (<0.1%)
Arthropod bite	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Eye injury	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Foot fracture	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Gun shot wound	0	1 (<0.1%)	0
Grade 4 (Life-Threatening)	0	1 (<0.1%)	0
Limb injury	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Pelvic fracture	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Radius fracture	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Rib fracture	0	1 (<0.1%)	0

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
Grade 3 (Severe)	0	1 (<0.1%)	0
Tendon injury	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Tibia fracture	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Toxicity to various agents	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Wound	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Investigations	10 (0.5%)	6 (0.3%)	5 (0.5%)
Grade 3 (Severe)	5 (0.2%)	6 (0.3%)	4 (0.4%)
Grade 4 (Life-Threatening)	5 (0.2%)	0	1 (<0.1%)
Blood creatine phosphokinase increased	3 (0.1%)	3 (0.1%)	0
Grade 3 (Severe)	2 (<0.1%)	3 (0.1%)	0
Grade 4 (Life-Threatening)	1 (<0.1%)	0	0
Creatinine renal clearance decreased	1 (<0.1%)	1 (<0.1%)	2 (0.2%)
Grade 3 (Severe)	1 (<0.1%)	1 (<0.1%)	2 (0.2%)
Hepatic enzyme increased	3 (0.1%)	0	0
Grade 4 (Life-Threatening)	3 (0.1%)	0	0
Alanine aminotransferase increased	0	0	1 (<0.1%)
Grade 4 (Life-Threatening)	0	0	1 (<0.1%)
Aspartate aminotransferase increased	0	0	1 (<0.1%)

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
Grade 3 (Severe)	0	0	1 (<0.1%)
Blood creatinine decreased	0	0	1 (<0.1%)
Grade 3 (Severe)	0	0	1 (<0.1%)
Blood pressure increased	1 (<0.1%)	0	0
Grade 4 (Life-Threatening)	1 (<0.1%)	0	0
Creatinine renal clearance abnormal	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Haemoglobin decreased	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Liver function test abnormal	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Low density lipoprotein increased	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Neutrophil count decreased	0	0	1 (<0.1%)
Grade 3 (Severe)	0	0	1 (<0.1%)
Weight decreased	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Metabolism and nutrition disorders	8 (0.4%)	3 (0.1%)	4 (0.4%)
Grade 3 (Severe)	7 (0.3%)	3 (0.1%)	3 (0.3%)
Grade 4 (Life-Threatening)	1 (<0.1%)	0	1 (<0.1%)
Abnormal loss of weight	8 (0.4%)	1 (<0.1%)	2 (0.2%)
Grade 3 (Severe)	7 (0.3%)	1 (<0.1%)	2 (0.2%)

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
Grade 4 (Life-Threatening)	1 (<0.1%)	0	0
Decreased appetite	0	0	1 (<0.1%)
Grade 3 (Severe)	0	0	1 (<0.1%)
Hyperlipidaemia	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Hypophosphataemia	0	0	1 (<0.1%)
Grade 4 (Life-Threatening)	0	0	1 (<0.1%)
Vitamin B12 deficiency	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Musculoskeletal and connective tissue disorders	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Back pain	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (<0.1%)	0
Grade 5 (Death)	0	1 (<0.1%)	0
Ovarian cancer	0	1 (<0.1%)	0
Grade 5 (Death)	0	1 (<0.1%)	0
Nervous system disorders	5 (0.2%)	4 (0.2%)	1 (<0.1%)
Grade 3 (Severe)	5 (0.2%)	4 (0.2%)	1 (<0.1%)
Syncope	2 (<0.1%)	2 (<0.1%)	0
Grade 3 (Severe)	2 (<0.1%)	2 (<0.1%)	0

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
Headache	1 (<0.1%)	2 (<0.1%)	0
Grade 3 (Severe)	1 (<0.1%)	2 (<0.1%)	0
Monoparesis	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Neuromyelitis optica spectrum disorder	0	0	1 (<0.1%)
Grade 3 (Severe)	0	0	1 (<0.1%)
Seizure	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Pregnancy, puerperium and perinatal conditions	24 (1.1%)	26 (1.2%)	16 (1.5%)
Grade 3 (Severe)	21 (1.0%)	25 (1.2%)	13 (1.2%)
Grade 4 (Life-Threatening)	3 (0.1%)	1 (<0.1%)	3 (0.3%)
Abortion spontaneous	10 (0.5%)	18 (0.8%)	7 (0.7%)
Grade 3 (Severe)	10 (0.5%)	18 (0.8%)	6 (0.6%)
Grade 4 (Life-Threatening)	0	0	1 (<0.1%)
Cephalo-pelvic disproportion	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Grade 3 (Severe)	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Gestational hypertension	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Grade 3 (Severe)	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Grade 4 (Life-Threatening)	1 (<0.1%)	0	0
Abortion missed	2 (<0.1%)	1 (<0.1%)	0
Grade 3 (Severe)	2 (<0.1%)	1 (<0.1%)	0
Foetal death	3 (0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
Grade 4 (Life-Threatening)	2 (<0.1%)	0	0
Ruptured ectopic pregnancy	1 (<0.1%)	2 (<0.1%)	0
Grade 3 (Severe)	1 (<0.1%)	1 (<0.1%)	0
Grade 4 (Life-Threatening)	0	1 (<0.1%)	0
Abortion incomplete	0	1 (<0.1%)	1 (<0.1%)
Grade 3 (Severe)	0	1 (<0.1%)	0
Grade 4 (Life-Threatening)	0	0	1 (<0.1%)
Foetal distress syndrome	1 (<0.1%)	0	1 (<0.1%)
Grade 3 (Severe)	1 (<0.1%)	0	1 (<0.1%)
Obstructed labour	0	0	2 (0.2%)
Grade 3 (Severe)	0	0	2 (0.2%)
Retained products of conception	1 (<0.1%)	0	1 (<0.1%)
Grade 3 (Severe)	1 (<0.1%)	0	1 (<0.1%)
Stillbirth	0	1 (<0.1%)	1 (<0.1%)
Grade 3 (Severe)	0	1 (<0.1%)	1 (<0.1%)
Abortion of ectopic pregnancy	0	0	1 (<0.1%)
Grade 4 (Life-Threatening)	0	0	1 (<0.1%)
Abortion spontaneous incomplete	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Abortion threatened	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Anembryonic gestation	0	1 (<0.1%)	0

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
Grade 3 (Severe)	0	1 (<0.1%)	0
Ectopic pregnancy	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Haemorrhage in pregnancy	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Hyperemesis gravidarum	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Polyhydramnios	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Prolonged labour	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Product issues	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Device dislocation	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Psychiatric disorders	7 (0.3%)	8 (0.4%)	0
Grade 3 (Severe)	6 (0.3%)	4 (0.2%)	0
Grade 4 (Life-Threatening)	1 (<0.1%)	4 (0.2%)	0
Intentional self-injury	2 (<0.1%)	4 (0.2%)	0
Grade 3 (Severe)	2 (<0.1%)	2 (<0.1%)	0
Grade 4 (Life-Threatening)	0	2 (<0.1%)	0
Suicide attempt	2 (<0.1%)	3 (0.1%)	0

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
Grade 3 (Severe)	1 (<0.1%)	1 (<0.1%)	0
Grade 4 (Life-Threatening)	1 (<0.1%)	2 (<0.1%)	0
Anxiety	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Depression	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Psychotic disorder	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Suicidal ideation	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Renal and urinary disorders	1 (<0.1%)	1 (<0.1%)	2 (0.2%)
Grade 3 (Severe)	1 (<0.1%)	1 (<0.1%)	2 (0.2%)
Glycosuria	1 (<0.1%)	1 (<0.1%)	0
Grade 3 (Severe)	1 (<0.1%)	1 (<0.1%)	0
Proteinuria	0	0	2 (0.2%)
Grade 3 (Severe)	0	0	2 (0.2%)
Reproductive system and breast disorders	0	2 (<0.1%)	0
Grade 4 (Life-Threatening)	0	2 (<0.1%)	0
Abnormal uterine bleeding	0	1 (<0.1%)	0
Grade 4 (Life-Threatening)	0	1 (<0.1%)	0
Threatened uterine rupture	0	1 (<0.1%)	0
Grade 4 (Life-Threatening)	0	1 (<0.1%)	0

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
Respiratory, thoracic and mediastinal disorders	0	2 (<0.1%)	4 (0.4%)
Grade 3 (Severe)	0	1 (<0.1%)	4 (0.4%)
Grade 5 (Death)	0	1 (<0.1%)	
Asthma	0	1 (<0.1%)	4 (0.4%)
Grade 3 (Severe)	0	1 (<0.1%)	4 (0.4%)
Asphyxia	0	1 (<0.1%)	0
Grade 5 (Death)	0	1 (<0.1%)	0
Skin and subcutaneous tissue disorders	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Grade 3 (Severe)	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Angioedema	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Dermatitis	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Dermatitis psoriasiform	1 (<0.1%)	0	0
Grade 3 (Severe)	1 (<0.1%)	0	0
Urticaria	0	0	1 (<0.1%)
Grade 3 (Severe)	0	0	1 (<0.1%)
Social circumstances	1 (<0.1%)	2 (<0.1%)	1 (<0.1%)
Grade 3 (Severe)	1 (<0.1%)	0	1 (<0.1%)
Grade 5 (Death)	0	2 (<0.1%)	0
Victim of homicide	0	2 (<0.1%)	0
Grade 5 (Death)	0	2 (<0.1%)	0

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)
Victim of sexual abuse	1 (<0.1%)	0	1 (<0.1%)
Grade 3 (Severe)	1 (<0.1%)	0	1 (<0.1%)
Vascular disorders	0	3 (0.1%)	0
Grade 3 (Severe)	0	2 (<0.1%)	0
Grade 5 (Death)	0	1 (<0.1%)	0
Haemorrhage	0	1 (<0.1%)	0
Grade 5 (Death)	0	1 (<0.1%)	0
Hypertension	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0
Superficial vein thrombosis	0	1 (<0.1%)	0
Grade 3 (Severe)	0	1 (<0.1%)	0

Adverse events coded according to Medical Dictionary for Regulatory Activities (MedDRA) 27.0 and graded by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. ISR: injection site reaction.

Table S11. Treatment-Emergent Serious Adverse Events

	Lenacapavir (N=2138)	F/TAF (N=2137)	F/TDF (N=1070)
Number (%) of Participants with Any Serious Adverse Events	59 (2.8%)	85 (4.0%)	35 (3.3%)
Blood and lymphatic system disorders	2 (<0.1%)	1 (<0.1%)	0
Hypochromic anaemia	2 (<0.1%)	0	0
Anaemia	0	1 (<0.1%)	0
Cardiac disorders	0	2 (<0.1%)	0
Ischaemic cardiomyopathy	0	1 (<0.1%)	0
Nonreassuring foetal heart rate pattern	0	1 (<0.1%)	0
Eye disorders	0	1 (<0.1%)	0
Cataract	0	1 (<0.1%)	0
Gastrointestinal disorders	0	2 (<0.1%)	3 (0.3%)
Gastritis	0	0	2 (0.2%)
Abdominal pain lower	0	0	1 (<0.1%)
Haematemesis	0	1 (<0.1%)	0
Peptic ulcer	0	1 (<0.1%)	0
Hepatobiliary disorders	0	1 (<0.1%)	0
Cholelithiasis	0	1 (<0.1%)	0
Infections and infestations	12 (0.6%)	16 (0.7%)	3 (0.3%)
Malaria	3 (0.1%)	5 (0.2%)	0
Urinary tract infection	1 (<0.1%)	3 (0.1%)	0
Appendicitis	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Hepatitis A	0	1 (<0.1%)	1 (<0.1%)
Brain empyema	1 (<0.1%)	0	0
Gastroenteritis	1 (<0.1%)	0	0
Helicobacter infection	1 (<0.1%)	0	0

	Lenacapavir (N=2138)	F/TAF (N=2137)	F/TDF (N=1070)
Injection site abscess	0	1 (<0.1%)	0
Lower respiratory tract infection	0	1 (<0.1%)	0
Pelvic inflammatory disease	0	1 (<0.1%)	0
Peritonitis	0	1 (<0.1%)	0
Pneumonia	0	1 (<0.1%)	0
Postoperative wound infection	0	1 (<0.1%)	0
Pyelonephritis	1 (<0.1%)	0	0
Pyelonephritis acute	1 (<0.1%)	0	0
Salpingitis	0	0	1 (<0.1%)
Sepsis	0	1 (<0.1%)	0
Sinusitis	1 (<0.1%)	0	0
Subcutaneous abscess	1 (<0.1%)	0	0
Tonsillitis	1 (<0.1%)	0	0
Injury, poisoning and procedural complications	9 (0.4%)	13 (0.6%)	5 (0.5%)
Overdose	3 (0.1%)	1 (<0.1%)	0
Road traffic accident	1 (<0.1%)	2 (<0.1%)	0
Ankle fracture	2 (<0.1%)	0	0
Humerus fracture	0	0	2 (0.2%)
Lower limb fracture	0	0	2 (0.2%)
Stab wound	0	2 (<0.1%)	0
Thermal burn	1 (<0.1%)	1 (<0.1%)	0
Anaemia postoperative	0	0	1 (<0.1%)
Animal bite	0	0	1 (<0.1%)
Eye injury	0	1 (<0.1%)	0
Foot fracture	1 (<0.1%)	0	0
Gun shot wound	0	1 (<0.1%)	0
Limb injury	1 (<0.1%)	0	0
Pelvic fracture	0	1 (<0.1%)	0
Radius fracture	0	1 (<0.1%)	0
Rib fracture	0	1 (<0.1%)	0

	Lenacapavir (N=2138)	F/TAF (N=2137)	F/TDF (N=1070)
Tendon injury	0	1 (<0.1%)	0
Tibia fracture	0	1 (<0.1%)	0
Toxicity to various agents	0	1 (<0.1%)	0
Investigations	1 (<0.1%)	0	0
Blood pressure increased	1 (<0.1%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (<0.1%)	0
Ovarian cancer	0	1 (<0.1%)	0
Nervous system disorders	4 (0.2%)	3 (0.1%)	1 (<0.1%)
Syncope	2 (<0.1%)	1 (<0.1%)	0
Headache	0	2 (<0.1%)	0
Monoparesis	1 (<0.1%)	0	0
Neuromyelitis optica spectrum disorder	0	0	1 (<0.1%)
Seizure	1 (<0.1%)	0	0
Pregnancy, puerperium and perinatal conditions	30 (1.4%)	37 (1.7%)	17 (1.6%)
Abortion spontaneous	15 (0.7%)	28 (1.3%)	9 (0.8%)
Abortion missed	2 (<0.1%)	2 (<0.1%)	0
Cephalo-pelvic disproportion	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Gestational hypertension	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Foetal death	3 (0.1%)	0	0
Ruptured ectopic pregnancy	1 (<0.1%)	2 (<0.1%)	0
Abortion incomplete	0	1 (<0.1%)	1 (<0.1%)
Anembryonic gestation	0	2 (<0.1%)	0
Foetal distress syndrome	1 (<0.1%)	0	1 (<0.1%)
Obstructed labour	0	0	2 (0.2%)
Stillbirth	0	1 (<0.1%)	1 (<0.1%)
Abortion of ectopic pregnancy	0	0	1 (<0.1%)
Abortion spontaneous complete	1 (<0.1%)	0	0

	Lenacapavir (N=2138)	F/TAF (N=2137)	F/TDF (N=1070)
Abortion spontaneous incomplete	1 (<0.1%)	0	0
Abortion threatened	0	1 (<0.1%)	0
Ectopic pregnancy	0	1 (<0.1%)	0
Haemorrhage in pregnancy	0	1 (<0.1%)	0
Hyperemesis gravidarum	1 (<0.1%)	0	0
Polyhydramnios	1 (<0.1%)	0	0
Pre-eclampsia	0	1 (<0.1%)	0
Prolonged labour	0	1 (<0.1%)	0
Retained products of conception	1 (<0.1%)	0	0
Product issues	1 (<0.1%)	0	0
Device dislocation	1 (<0.1%)	0	0
Psychiatric disorders	6 (0.3%)	8 (0.4%)	0
Intentional self-injury	2 (<0.1%)	4 (0.2%)	0
Suicide attempt	2 (<0.1%)	3 (0.1%)	0
Depression	1 (<0.1%)	0	0
Psychotic disorder	1 (<0.1%)	0	0
Suicidal ideation	0	1 (<0.1%)	0
Renal and urinary disorders	0	0	1 (<0.1%)
Proteinuria	0	0	1 (<0.1%)
Reproductive system and breast disorders	0	2 (<0.1%)	0
Abnormal uterine bleeding	0	1 (<0.1%)	0
Threatened uterine rupture	0	1 (<0.1%)	0
Respiratory, thoracic and mediastinal disorders	0	2 (<0.1%)	4 (0.4%)
Asthma	0	1 (<0.1%)	4 (0.4%)
Asphyxia	0	1 (<0.1%)	0
Social circumstances	1 (<0.1%)	2 (<0.1%)	1 (<0.1%)

	Lenacapavir (N=2138)	F/TAF (N=2137)	F/TDF (N=1070)
Victim of homicide	0	2 (<0.1%)	0
Victim of sexual abuse	1 (<0.1%)	0	1 (<0.1%)
Vascular disorders	0	3 (0.1%)	0
Haemorrhage	0	1 (<0.1%)	0
Hypertension	0	1 (<0.1%)	0
Superficial vein thrombosis	0	1 (<0.1%)	0

Adverse events coded according to Medical Dictionary for Regulatory Activities (MedDRA) 27.0 and graded by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. No participants had a serious injection site reaction.

Table S12. Treatment-Emergent Adverse Events Leading to Premature Study Drug Discontinuation

	Lenacapavir (N=2138)	F/TAF (N=2137)	F/TDF (N=1070)
Number (%) of Participants with Any Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (Excluding ISRs)	5 (0.2%)	2 (<0.1%)	0
Number (%) of Participants with Any Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (Including ISRs)	9 (0.4%)	2 (<0.1%)	0
Gastrointestinal disorders	1 (<0.1%)	0	0
Nausea	1 (<0.1%)	0	0
General disorders and administration site conditions	4 (0.2%)	0	0
Injection site nodule	4 (0.2%)	0	0
Injection site pain	1 (<0.1%)	0	0
Injury, poisoning and procedural complications	0	1 (<0.1%)	0
Overdose	0	1 (<0.1%)	0
Investigations	2 (<0.1%)	0	0
Creatinine renal clearance decreased	1 (<0.1%)	0	0
Hepatic enzyme increased	1 (<0.1%)	0	0
Pregnancy, puerperium and perinatal conditions	1 (<0.1%)	0	0
Abortion spontaneous	1 (<0.1%)	0	0
Psychiatric disorders	1 (<0.1%)	1 (<0.1%)	0
Suicide attempt	1 (<0.1%)	1 (<0.1%)	0
Depressive symptom	0	1 (<0.1%)	0
Major depression	1 (<0.1%)	0	0
Skin and subcutaneous tissue disorders	0	1 (<0.1%)	0
Angioedema	0	1 (<0.1%)	0

Adverse events coded according to Medical Dictionary for Regulatory Activities (MedDRA) 27.0 and graded by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. ISR: injection site reaction.

Table S13. Grade 3 and 4 Treatment-Emergent Laboratory Abnormalities

Maximum Postbaseline Toxicity Grade	Lenacapavir (N=2138)	F/TAF (N=2137)	F/TDF (N=1070)
Participants with Postbaseline Value	2126	2113	1054
Grade 3 or 4	112 (5.3%)	103 (4.9%)	61 (5.8%)
Grade 3	92 (4.3%)	81 (3.8%)	50 (4.7%)
Grade 4	20 (0.9%)	22 (1.0%)	11 (1.0%)
Hematology			
Hemoglobin (Decreased)	2126	2112	1054
Grade 3 or 4	8 (0.4%)	5 (0.2%)	5 (0.5%)
Grade 3	6 (0.3%)	5 (0.2%)	5 (0.5%)
Grade 4	2 (<0.1%)	0	0
Lymphocytes (Decreased)	2122	2111	1054
Grade 3 or 4	2 (<0.1%)	4 (0.2%)	2 (0.2%)
Grade 3	2 (<0.1%)	2 (<0.1%)	1 (<0.1%)
Grade 4	0	2 (<0.1%)	1 (<0.1%)
Platelets (Decreased)	2126	2112	1053
Grade 3 or 4	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0
WBC (Decreased)	2126	2112	1054
Grade 3 or 4	0	0	1 (<0.1%)
Grade 3	0	0	1 (<0.1%)
Grade 4	0	0	0
Chemistry			
Albumin (Decreased)	2125	2113	1054
Grade 3 or 4	0	0	0

	Lenacapavir	F/TAF	F/TDF
Grade 3	0	0	0
Grade 4	0	0	0
Alkaline Phosphatase (Increased)	2125	2113	1054
Grade 3 or 4	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0
ALT (Increased)	2125	2113	1054
Grade 3 or 4	12 (0.6%)	6 (0.3%)	1 (<0.1%)
Grade 3	6 (0.3%)	2 (<0.1%)	0
Grade 4	6 (0.3%)	4 (0.2%)	1 (<0.1%)
AST (Increased)	2125	2113	1054
Grade 3 or 4	8 (0.4%)	7 (0.3%)	2 (0.2%)
Grade 3	4 (0.2%)	3 (0.1%)	1 (<0.1%)
Grade 4	4 (0.2%)	4 (0.2%)	1 (<0.1%)
Bicarbonate (Decreased)	2125	2113	1054
Grade 3 or 4	0	1 (<0.1%)	0
Grade 3	0	1 (<0.1%)	0
Grade 4	0	0	0
Corrected Calcium (Hypercalcemia)	2125	2113	1054
Grade 3 or 4	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0
Corrected Calcium (Hypocalcemia)	2125	2113	1054
Grade 3 or 4	2 (<0.1%)	5 (0.2%)	3 (0.3%)
Grade 3	2 (<0.1%)	4 (0.2%)	2 (0.2%)
Grade 4	0	1 (<0.1%)	1 (<0.1%)

	Lenacapavir	F/TAF	F/TDF
Creatine Kinase (Increased)	2125	2113	1054
Grade 3 or 4	28 (1.3%)	25 (1.2%)	12 (1.1%)
Grade 3	18 (0.8%)	15 (0.7%)	8 (0.8%)
Grade 4	10 (0.5%)	10 (0.5%)	4 (0.4%)
Creatinine (Increased)	2125	2113	1054
Grade 3 or 4	13 (0.6%)	10 (0.5%)	10 (0.9%)
Grade 3	12 (0.6%)	10 (0.5%)	9 (0.9%)
Grade 4	1 (<0.1%)	0	1 (<0.1%)
Creatinine Clearance (Decreased)	2125	2113	1054
Grade 3 or 4	41 (1.9%)	36 (1.7%)	23 (2.2%)
Grade 3	41 (1.9%)	35 (1.7%)	22 (2.1%)
Grade 4	0	1 (<0.1%)	1 (<0.1%)
Direct Bilirubin (Hyperbilirubinemia)	2125	2113	1054
Grade 3 or 4	8 (0.4%)	5 (0.2%)	2 (0.2%)
Grade 3	8 (0.4%)	5 (0.2%)	2 (0.2%)
Grade 4	0	0	0
Lipase (Increased)	2125	2113	1054
Grade 3 or 4	2 (<0.1%)	0	1 (<0.1%)
Grade 3	1 (<0.1%)	0	1 (<0.1%)
Grade 4	1 (<0.1%)	0	0
Magnesium (Hypomagnesemia)	2125	2113	1054
Grade 3 or 4	6 (0.3%)	10 (0.5%)	5 (0.5%)
Grade 3	6 (0.3%)	7 (0.3%)	3 (0.3%)
Grade 4	0	3 (0.1%)	2 (0.2%)
Phosphate (Hypophosphatemia)	2125	2113	1053
Grade 3 or 4	2 (<0.1%)	2 (<0.1%)	1 (<0.1%)

	Lenacapavir	F/TAF	F/TDF
Grade 3	2 (<0.1%)	2 (<0.1%)	0
Grade 4	0	0	1 (<0.1%)
Serum Glucose (Fasting, Hyperglycemia)	2013	2001	999
Grade 3 or 4	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0
Serum Glucose (Nonfasting, Hyperglycemia, Maximum Postbaseline Grade	1879	1853	904
Grade 3 or 4	0	1 (<0.1%)	0
Grade 3	0	1 (<0.1%)	0
Grade 4	0	0	0
Serum Glucose (Hypoglycemia)	2125	2113	1053
Grade 3 or 4	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Grade 3	1 (<0.1%)	1 (<0.1%)	0
Grade 4	0	0	1 (<0.1%)
Serum Potassium (Hyperkalemia)	2125	2113	1053
Grade 3 or 4	0	3 (0.1%)	2 (0.2%)
Grade 3	0	0	2 (0.2%)
Grade 4	0	3 (0.1%)	0
Serum Potassium (Hypokalemia)	2125	2113	1053
Grade 3 or 4	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0
Serum Sodium (Hypernatremia)	2125	2113	1054
Grade 3 or 4	0	0	0
Grade 3	0	0	0

	Lenacapavir	F/TAF	F/TDF
Grade 4	0	0	0
Serum Sodium (Hyponatremia)	2125	2113	1054
Grade 3 or 4	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0
Total Bilirubin (Hyperbilirubinemia)	2125	2113	1054
Grade 3 or 4	1 (<0.1%)	2 (<0.1%)	0
Grade 3	1 (<0.1%)	2 (<0.1%)	0
Grade 4	0	0	0
Total Cholesterol (Fasting, Hypercholesterolemia)	1936	1914	946
Grade 3 or 4	0	2 (0.1%)	0
Grade 3	0	2 (0.1%)	0
Grade 4	0	0	0
Triglycerides (Fasting, Increased)	1936	1914	946
Grade 3 or 4	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0
LDL (Fasting, Increased)	1936	1914	946
Grade 3 or 4	0	4 (0.2%)	0
Grade 3	0	4 (0.2%)	0
Grade 4	0	0	0
Uric Acid (Hyperuricemia)	2125	2113	1054
Grade 3 or 4	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0

	Lenacapavir	F/TAF	F/TDF
Urinalysis			
Urine Glucose (Glycosuria)	2125	2112	1054
Grade 3	4 (0.2%)	4 (0.2%)	0
Urine Protein (Proteinuria)	2125	2112	1054
Grade 3	4 (0.2%)	6 (0.3%)	9 (0.9%)
Urine RBC (Hematuria, Quantitative)	2125	2112	1054
Grade 3 or 4	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0

For non-fasting 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.
Urinalysis: urine protein and urine glucose highest grade is Grade 3. Fasting metabolic assessments are collected at Day 1, Week 26 and every 26 weeks.
Graded by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1.

Table S14: Pregnancy Outcomes

	Lenacapavir (N = 2138)	F/TAF (N = 2137)	F/TDF (N = 1070)	Total (N = 5345)
Number of participants with confirmed pregnancies	184	208	95	487
Number of confirmed pregnancies	193	219	98	510
Completed pregnancies — no. (%)	105 (54.4)	119 (54.3)	53 (54.1)	277 (54.3)
Ongoing pregnancies	88 (45.6)	100 (45.7)	45 (45.9)	233 (45.7)
Births[a]	55 (28.5)	45 (20.5)	21 (21.4)	121 (23.7)
Interrupted pregnancies — no. (%)	50 (25.9)	74 (33.8)	32 (32.7)	156 (30.6)
Spontaneous abortion[b] — no. (%)	20 (10.4)	34 (15.5)	12 (12.2)	66 (12.9)
Induced abortion — no. (%)	30 (15.5)	40 (18.3)	20 (20.4)	90 (17.6)

Expected spontaneous abortion rate is 10-20% of clinically recognized pregnancies and approximately 30% of biochemically detected pregnancies.[18-20]

[a] Completed uninterrupted pregnancies which includes live births and 8 still births: 3 in the lenacapavir group, 4 in the F/TAF group, and 1 in the F/TDF group.

[b] Spontaneous abortion defined as occurring at <20 weeks' gestation.

Table S15. Participants in PURPOSE 1 Reflect Cisgender Women 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	There are 1.3 million new cases of HIV infection per year globally, of which cisgender women account for 47% (610,000 of 1,300,000). In Sub-Saharan Africa, cisgender women and girls represent 63% of new annual HIV infections (418,000 of 660,000). Among people aged 15-24 years in Sub-Saharan Africa, 77% are women (162,000 of 210,000).
Age	27% of global infections (350,000 of 1,300,000), and 32% of new infections in Sub-Saharan Africa (210,000 of 660,000), are in people aged 15-24 years.
Race or ethnic group	51% of global infections are in Sub-Saharan Africans. This trial was carried out in South Africa and Uganda, and virtually all (99.9%) of participants were Black. The remainder were Multiracial (in South Africa).
Geography	51% of global infections are in Sub-Saharan Africa, which includes South Africa and Uganda.
Other considerations	We included pregnant and lactating women and adolescents, both groups are disproportionately affected by HIV infection
Overall representativeness of this trial	The participants in the present trial are representative of young women and girls in South Africa and Uganda who have high likelihood of HIV acquisition and are living in areas with high HIV incidence and demonstrated the expected racial distribution.

References

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