Supplementary Appendix

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

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Supplementary Background

Non-human primate (NHP) models have demonstrated that CAB LA can protect against rectal, vaginal, parenteral, and penile SIV and SHIV challenges.[1-5] In those studies, high levels of protection were seen against repeated exposures when CAB plasma concentrations were above 4-times the protein-adjusted (PA) IC_{90} (0.664 µg/mL), and were maintained at drug concentrations above the PA-IC_{90} (0.166 µg/mL).

In Phase 2 and 3 HIV treatment studies evaluating long-acting cabotegravir in combination with long-acting rilpivirine for maintenance of virologic suppression among participants who had not previously failed an HIV treatment regimen, virologic failures were infrequent. When virologic failure occurred, in addition to NNRTI-associated mutations, resistance associated mutations were found in the integrase gene of Q148R or N155H with or without accessory mutations including combinations of L74I and G140R. These variably conferred cross resistance to CAB, raltegravir, and elvitegravir, and lower-level resistance to dolutegravir and bictegravir.[6-8] Non-human primate models of acute or primary SHIV infection in which CAB LA was administered during acute viremia generated integrase resistance mutations conferring varying levels of integrase-class resistance as well as decreased replicative capacity.[9] These observations raised the concern that CAB PrEP breakthrough may also be associated with CAB and/or other-integrase resistant virus, and may compromise the efficacy of global first-line integrase-based ART treatment regimens.

For persons living with HIV, ART that contains an integrase inhibitor has been associated with weight gain and increased waist circumference, with changes of greater magnitude seen among women, black patients, and those with lower CD4 and higher HIV RNA prior to starting ART. Some studies have found a mitigating effect of TDF (vs. TAF or ABC) in the ART regimen. While the mechanism of these changes remains elusive in the complex inflammatory milieu of HIV disease, the HIV prevention setting provides a unique opportunity to evaluate weight changes attributable to components of these ART

regimens appropriate for PrEP absent HIV infection. In a Phase 2 randomized comparison of CAB LA and a saline placebo, we found a non-significantly different approximately 1.0 kg weight gain in each study arm over 41 weeks.[10] Similarly, in a Phase 3 randomized double-blind comparison of TAF/FTC and TDF/FTC, a 1.1 kg weight gain was observed compared to -0.1 kg, respectively over 48 weeks.[11]

Supplementary Methods

Detailed methods used for HIV testing and endpoint adjudication are provided in Marzinke et al, JID, 2021[12]. Pre-planned site-based HIV testing and retrospective, centralized HIV testing performed at the HPTN Laboratory Center are described briefly below. Additional information about this testing and information about expanded post-hoc centralized HIV testing are described in Marzinke et al JID 2021[12].

Adherence and Risk Reduction Counseling Approach

LifeSteps was initially conceptualized as a single session treatment adherence intervention for persons living with HIV[13,14], though has since been adapted for individuals who wish to use pre-exposure prophylaxis (PrEP) across several international and domestic contexts[15-17]. LifeSteps is based on principles of cognitive behavioral therapy for health behavior change, with an emphasis on motivational strategies and problem-solving skills, and assumes that there are several steps in which people need to engage in order to be effective consumers of medication, including having a medication taking schedule, getting to appointments, a plan for communication with healthcare providers and managing side effects, and a plan for obtaining refills and storing medications. Individuals then develop a plan and back-up for each of these key behaviors. Participants in HPTN 083 engaged in an initial adherence counseling session that included a review of the study design and the definitions of adherence for both oral study product and injections. Participants also developed plans for each of the key steps in LifeSteps, for both oral study product and injections. Subsequent LifeSteps adherence counseling sessions focused on perceived effectiveness of these plans, and adjustments were made as needed, based on participant preferences and effectiveness. For participants who encountered ongoing challenges to adherence (as assessed by the study interventionist), more in-depth counseling and problem-solving of key barriers to adherence was provided, using a framework based on problem-solving

therapy[18]. Participants were also encouraged to anticipate barriers to adherence that might occur between counseling sessions, and develop plans for those (e.g., travel, change in work schedule). For additional information about LifeSteps and the manual, as recognized by the CDC as an evidenced-based PrEP adherence intervention, please see Psaros et al., 2020[19,20]

Site Testing

HIV viral load testing was performed for all participants within 14 days prior to enrollment; participants with positive results were not eligible for enrollment. Testing at each study visit included HIV rapid (point-of-care) antibody testing using an assay approved by the United States Food and Drug Administration (US FDA) and instrument-based antigen/antibody testing. HIV infection was confirmed for samples that had reactive or positive results for one or both of these tests. When possible, samples from two different dates were used to confirm HIV infection. In some cases where it was difficult to determine HIV status, peripheral blood mononuclear cell (PBMC) samples were tested in real-time at the HPTN Laboratory Center using an ultra-sensitive HIV DNA test. A centralized committee, firewalled from the study team, reviewed all site HIV test results in real time and provided guidance for additional HIV testing and clinical management.

Centralized Testing

In all cases where a reactive or positive HIV test was obtained at a study site, additional HIV testing was performed retrospectively at the HPTN Laboratory Center to determine HIV infection status and the timing of HIV infection. The primary algorithm for this testing included an instrument-based antigen/antibody assay, a discriminatory antibody assay, and a qualitative HIV RNA test. Where possible, HIV infection was confirmed using samples collected at two study visits. The pre-specified HIV testing algorithm included “back testing” using the qualitative HIV RNA assay; this testing was performed for the first visit where the site had a reactive or positive test, and at prior visits until a

negative test result was obtained. Samples with reactive qualitative HIV RNA test results at the visits noted and subsequent study visits were tested with a viral load assay. HIV genotyping was performed retrospectively for selected samples that had viral loads >500 copies/mL.

Statistical Analysis

The HPTN 083 protocol initially specified an interim monitoring plan for efficacy based on crossing the O'Brien-Fleming superiority boundary, a supererogatory criterion in a non-inferiority trial. Beginning in mid-March 2020, COVID-19 related site closures and staffing restrictions created the potential for delays in dispensing of blinded study drug and injections and in timely capture of outcome information in a substantial fraction of sites. Study leadership became concerned about the potential for bias in the evaluation of intervention effect. Because of these concerns about COVID disruption to study execution, the blinded study team proposed that the interim monitoring guidelines for termination be modified to require that evidence of benefit be sufficient to cross a non-inferiority boundary rather than requiring crossing a superiority boundary. This change would enable the study to be terminated as soon as persuasive evidence of efficacy had been achieved (i.e., by crossing the non-inferiority boundary), and decreased the potential risk, through early termination, of relying on evidence that could be impacted by COVID disruptions. This revision was endorsed by the blinded and independent HPTN study monitoring committee, including the sponsor, NIAID. The NIAID DSMB acknowledged the change on April 4, 2020.

At the time of the first interim review, May 14, 2020, the study had crossed the non-inferiority boundary for benefit, and the DSMB recommending stopping the blinded portion of the study. Of note, because the O'Brien-Fleming threshold for stopping at the first interim visit is highly conservative (early stopping requires a p-value less than 0.0001 relative to the non-inferiority hypothesis HR=1.23), the final study result ruled out HR=1.0 using a 95% confidence interval (0.18, 0.62) that has proper coverage probability when adjusting for the group sequential testing, providing a definitive superiority result.

Potential participants were excluded from eligibility for HPTN 083 if they reported history of seizures or if they had chronic hepatitis B infection (as evidenced by a positive hepatitis B surface antigen test) or serologic evidence of current or past HCV infection (as evidenced by a reactive hepatitis C antibody). Those with a history of seizures were excluded after a small number of seizures were reported during the CAB development program (both HIV treatment and PrEP), prompting exclusion and enhanced reporting in the Phase 3 studies for PrEP. Hepatotoxicity was considered an event of special interest and closely monitored due to the risk of elevated transaminases observed with other integrase strand transfer inhibitors, and after six participants across the CAB development program developed suspected drug induced liver injury after exposure to oral cabotegravir; no participant receiving CAB LA has developed suspected drug induced liver injury attributable to CAB to-date. Out of an abundance of caution, participants with a history of pre-existing liver disease including steatosis or viral hepatitis were therefore excluded.

Supplementary Results

Charter for Syphilis Adjudication

I. Background:

Historically, syphilis and HIV infection have been closely linked among men who have sex with men (MSM) and transgender women (TGW), with rates of HIV coinfection as high as 70% in those newly diagnosed with syphilis.[1] In addition, multiple analyses have shown that MSM are at greater risk for HIV diagnosis after being diagnosed with early syphilis.[2,3] HIV pre-exposure prophylaxis (PrEP) has helped to dissociate this link: PrEP studies in research and clinical settings have demonstrated drastically reduced incidence of HIV despite high rates of syphilis and other sexually transmitted infections (STIs).[4–6] However, even in the setting of PrEP, syphilis infection continues to be associated with HIV acquisition in HIV negative MSM.[7] High rates of syphilis are anticipated in HPTN 083, and careful surveillance during the study is critical to gain an accurate understanding of syphilis prevalence, and more importantly, syphilis incidence. With broad geographic diversity and expertise in syphilis test result interpretation, HPTN 083's sites have wide heterogeneity in terms of laboratory testing used (VDRL vs. RPR) and diagnostic algorithm employed (traditional vs. reverse sequence). Indications for treatment also differ at the local level, as does the regimen for treatment depending on stage of disease. Thus, a standardized approach to the interpretation of syphilis testing is needed to maintain internal consistency within the study, and ensure that titers are interpreted and generate treatment responses that are harmonized across sites. In order to harmonize reactive test interpretation, treatment paradigms, and disease state (prevalent, incident, serofast without acute disease) coding during the study, the CMC has elected to evaluate all reactive testing results prospectively, beginning at enrollment and throughout study follow-up. In addition, this manner of prospectively monitoring syphilis events will greatly facilitate data cleaning, avoiding the burden of post-hoc interpretation of a large number of tests, and the requirement for significant investment of resources both at the site and protocol team level. However, this process is greatly facilitated by common understanding of the expectations of the site reports as indicated below.

II. Role of the CMC

Guidelines for the diagnosis and management of syphilis are published every 4-5 years by the US Centers for Disease Control and Prevention (CDC).[8] The CMC follows these guidelines in directing sites when management questions arise. Notably, the CMC also requests that sites obtain outside records when possible to confirm that the current non-treponemal test titer results are correctly contextualized and that management is appropriate. Correspondence with the CMC also ensures that follow-up testing is appropriately scheduled, and that the same EQA-validated laboratory tests are used to interpret serial results. Importantly, the CMC offers guidance as to how to code the reactive syphilis testing results on the corresponding e-CRF. Per protocol, sites must contact the CMC whenever reactive syphilis results are received.

It should be noted that in the interest of assuring that all prevalent disease has been adequately treated at study entry, in order to best identify incident disease during study conduct, decisions regarding treatment will be intentionally conservative, erring on the side of possible over treatment at study entry when clinical scenarios are unclear based on missing or unobtainable clinical and laboratory details of prior disease, titers, testing, and/or treatment.

III. Objective:

The purpose of this document is to document the decision-making process of the Clinical Management Committee (CMC) of reactive syphilis testing in HPTN 083.

IV. Clinical Scenarios:

A. Pre-existing syphilis – reactive testing at Visit 2.0/W0/study entry:

#1: Newly diagnosed (prevalent) syphilis at study entry – the ppt has no prior history of syphilis diagnosis or treatment, or prior testing has been non-reactive
Ex of lab results: Reactive non-treponemal (RPR or VDRL) and reactive treponemal testing
Documentation: Pre-existing/prevalent syphilis
Treatment: For early vs late disease depending on time frame, per CDC guidelines
Follow-up: Three months (W17)

#2: Newly diagnosed (prevalent) syphilis at study entry – the ppt has no prior history of syphilis diagnosis or treatment, or prior testing has been non-reactive
Ex of lab results: Non-reactive non-treponemal (RPR or VDRL) and reactive treponemal testing
Documentation: Pre-existing/prevalent syphilis
Treatment: For early vs late disease depending on time frame, per CDC guidelines
Follow-up: Per Schedule of Evaluations (SOE)

#3: Newly diagnosed syphilis (prevalent) at study entry—the ppt has no prior history of syphilis diagnosis or treatment, or prior testing has been non-reactive
Ex of lab results: Reactive non-treponemal (RPR or VDRL) and non-reactive treponemal testing*
Documentation: Pre-existing/prevalent syphilis upon enrollment
Treatment: If RPR or VDRL titer is ≥1:2 then treat for early vs late disease depending on time frame, per CDC guidelines. For 1:1 titer non-treponemal results, false positive testing is more likely, and treatment is not obligated.
Follow-up: three months (W17)
**In some settings this combination would be considered false positive testing; however, because of the pre-test probability of syphilis in the HPTN 083 population, and a desire to err on the side of assurance that study-entry prevalent disease has been appropriately treated so as to best identify on-study incident cases (see above), the CMC recommends treatment in these scenarios.*

#4: Prior diagnosis of syphilis noted at study entry – the ppt has a prior history of syphilis diagnosis and treatment
Ex of lab results: Reactive non-treponemal (RPR or VDRL) and reactive treponemal testing. In this case, prior records with titers would be needed to confirm adequate treatment response, defined as a 4-fold reduction (that is, by two dilutions, e.g., from 1:64 to 1:16 or from 1:8 to 1:2) in pre-treatment titer.[§]
Documentation: Pre-existing/treated syphilis.
Treatment: None.

#3: Newly diagnosed syphilis at follow-up, ppt is asymptomatic, and titers are performed at an outside facility
Ex of lab results: Reactive non-treponemal (RPR or VDRL) and reactive treponemal testing. Non-treponemal titers are newly reactive, or have increased by at least 4-fold or not diminished from prior titer values by at least 4-fold in response to treatment.
Documentation: Interim visit for the date of the outside facility visit, and incident syphilis on the STI eCRF and AE forms, logged for the date of the outside facility visit.
Treatment: For early syphilis per CDC guidelines
Follow-up: Repeat titers in 3 months, or per SOE, whichever comes first.

#4: Newly diagnosed syphilis at follow-up, ppt has symptoms of primary or secondary syphilis, and testing is performed at an outside facility
Ex of lab results: Most often, reactive non-treponemal (RPR or VDRL) and reactive treponemal testing. In some cases of primary syphilis (e.g. presentation with chancre), false-negative testing may occur.
Documentation: Interim visit for the date of the outside facility visit, and incident syphilis on the STI eCRF and AE forms, logged for the date of the outside facility visit.
Treatment: For early syphilis
Follow-up: Repeat titers in 3 months, or per SOE, whichever comes first.

C. Follow-up reporting (performed at three months intervals after initial diagnosis/treatment, or per SOE)

#1: Previously diagnosed syphilis, treated with adequate response
Ex of lab results: Reactive or non-reactive non-treponemal (RPR or VDRL) and reactive treponemal testing. Non-treponemal titers have declined 4-fold (two dilutions) or more since the time of the initial treatment, or there has been seroreversion (non-treponemal titers now non-reactive).
Documentation: No eCRF/AE form completed
Treatment: None
Follow-up: Per SOE

#2: Previously diagnosed syphilis, treated with inadequate regimen or inadequate response
Ex of lab results: Reactive non-treponemal testing (RPR or VDRL) and reactive treponemal testing. Non-treponemal titer has increased or failed to decline 4-fold.
Documentation: Prevalent syphilis if considered ongoing from study entry, incident syphilis for cases in which reinfection is presumed.
Treatment: If more than 3-6 months have passed since the initial treatment, retreatment should occur (for late disease) and CSF evaluation should be considered. If less than 3 months have passed since initial treatment, then ppt would still be followed with titers for adequate response (unless re-exposure/reinfection is considered more likely, then retreatment would be requested).
Follow-up: Three months or per SOE, whichever comes first.

Follow-up: Per SOE
[§]*If prior records of titers cannot be obtained, but the titer upon study entry is low level (1:8 or less), this can be considered a serofast response if the site is able to document prior treatment or the ppt clearly remembers treatment history. However, in the setting of higher titers, reinfection is considered more likely and retreatment is recommended (see above approach description in scenarios that are unclear).*

#5: Prior diagnosis of syphilis noted at study entry, treated with inadequate regimen or inadequate response
Ex of lab results: Reactive non-treponemal testing (RPR or VDRL) and reactive treponemal testing. Non-treponemal titer has increased or failed to decline 4-fold.
Documentation: Pre-existing/prevalent syphilis upon enrollment
Treatment: If more than 3-6 months have passed since the initial treatment, retreatment should occur (for late disease) and CSF evaluation should be considered. If less than 3 months have passed since initial treatment, then ppt would still be followed with titers for adequate response (unless re-exposure/reinfection is considered more likely, then retreatment would be requested).
Follow-up: Three months (W17).

#6: Prior diagnosis of syphilis noted at study entry – the ppt has a prior history of syphilis diagnosis and treatment
Ex of lab results: Non-reactive non-treponemal (RPR or VDRL) and reactive treponemal testing. Prior records would still be requested to confirm previous treatment history, if available.
Documentation: Pre-existing/treated syphilis
Treatment: None
Follow-up: Per SOE

B. Incident syphilis:

#1: Newly diagnosed syphilis at follow-up, ppt is asymptomatic and testing is done per SOE
Ex of lab results: Reactive non-treponemal (RPR or VDRL) and reactive treponemal testing. Non-treponemal titers are newly reactive, or have increased by 4-fold or not diminished from prior titer values by 4-fold after treatment.
Documentation: Incident syphilis on the STI eCRF and AE forms
Treatment: For early syphilis per CDC guidelines
Follow-up: Repeat titers in 3 months

#2: Newly diagnosed syphilis at follow-up, ppt has symptoms of primary or secondary syphilis
Ex of lab results: Most often, reactive non-treponemal (RPR or VDRL) and reactive treponemal testing. In some cases of primary syphilis (e.g., presentation with chancre), false-negative testing may occur.
Documentation: Incident syphilis on the STI eCRF and AE forms
Treatment: For early syphilis per CDC guidelines
Follow-up: Repeat titers in 3 months or per SOE, whichever comes first

#3: Previously diagnosed syphilis, treated with adequate response, then with subsequent increase in titer

Ex of lab results: As an example, RPR 1:32, then 1:2 after appropriate treatment, then 1:8 or higher on follow-up[#]

Documentation: Incident syphilis

Treatment: For reinfection per CDC guidelines, likely for early syphilis if clear documentation that increase in titer is new. Sites are also to consider the possibility of treatment failure, assess for neurologic symptoms, and consider neurosyphilis with CNS evaluation when appropriate.

Follow-up: Three months or per SOE, whichever comes first.

[#]In cases of rising titer, when titer is still low-level and less than a four-fold increase from prior (e.g. 1:2 then 1:4), retreatment may not be required if there is no concern for re-exposure. In these cases, retesting within 3 months is requested.

#4 Previously diagnosed syphilis, treated with adequate response, and titers are performed at an outside facility

Ex of lab results: Reactive non-treponemal (RPR or VDRL) and reactive treponemal testing, with non-treponemal titer stable or decreasing from prior

Documentation: None required

Treatment: None

Follow-up: Per SOE

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Supplementary Discussion

The low HIV incidence rate observed in both treatment groups is unlikely to be attributable to absence of exposures capable of transmitting HIV infection. This assertion is supported by high rates of prevalent STIs at baseline (Table S4) and high rates of incident syphilis (16.7 per 100 PY) and rectal gonorrhea (11 per 100 PY) and rectal chlamydia (16.8 per 100 PY) [Table S5]. The DISCOVER trial, comparing daily oral F/TAF to daily oral F/TDF among MSM and TGW similarly found rates of rectal gonorrhea (21.6 and 20.5 per 100 PY respectively) and rectal chlamydia (27.5 and 28.2 per 100 PY respectively), with syphilis incidence rates of 10.5 and 9.2 per 100 PY respectively [FDA CDER Application Package Application number 208215Orig1s012]. Although in some series rectal gonorrhea incidence has been shown to correlate with HIV incidence, and in fact has been proposed as a surrogate marker of counterfactual HIV incidence[21], increases in ART scale-up have threatened to uncouple these metrics[22].

The differences in annual weight gain observed between the CAB and TDF/FTC arms is largely driven, as has been seen in DISCOVER[11], by early weight loss in the TDF/FTC arm. In HPTN 083, subsequent to the first year, annualized weight gain is similar between the two arms at approximately 1 kg per year. Interestingly an analysis of weight changes in the Kaiser Permanente system showed that persons living with HIV on ART (all types) gained 0.22 kg per year compared to 0.09 kg per year for matched HIV-uninfected controls. In contrast the ADVANCE study, a randomized trial of initial ART for HIV found that males experienced approximately a 4.7 kg weight gain over the first 48 weeks on a regimen of TAF/FTC/DTG, compared to approximately 3.0 kg for TDF/FTC/DTG and 0.5 kg for TDF/FTC, EFV.[23]

It is particularly notable that the HPTN 083 study population includes just under 50% of the US enrollment from Black/African American participants, 12.4% of the total population from transgender women, and 67.5% of the total population under age 30 – populations disproportionately affected by

HIV and least likely to benefit from currently available oral PrEP strategies. The consistency of the overall results both in direction and magnitude for these key subpopulations is encouraging that CAB LA has the potential to reduce population-level HIV incidence among these communities.

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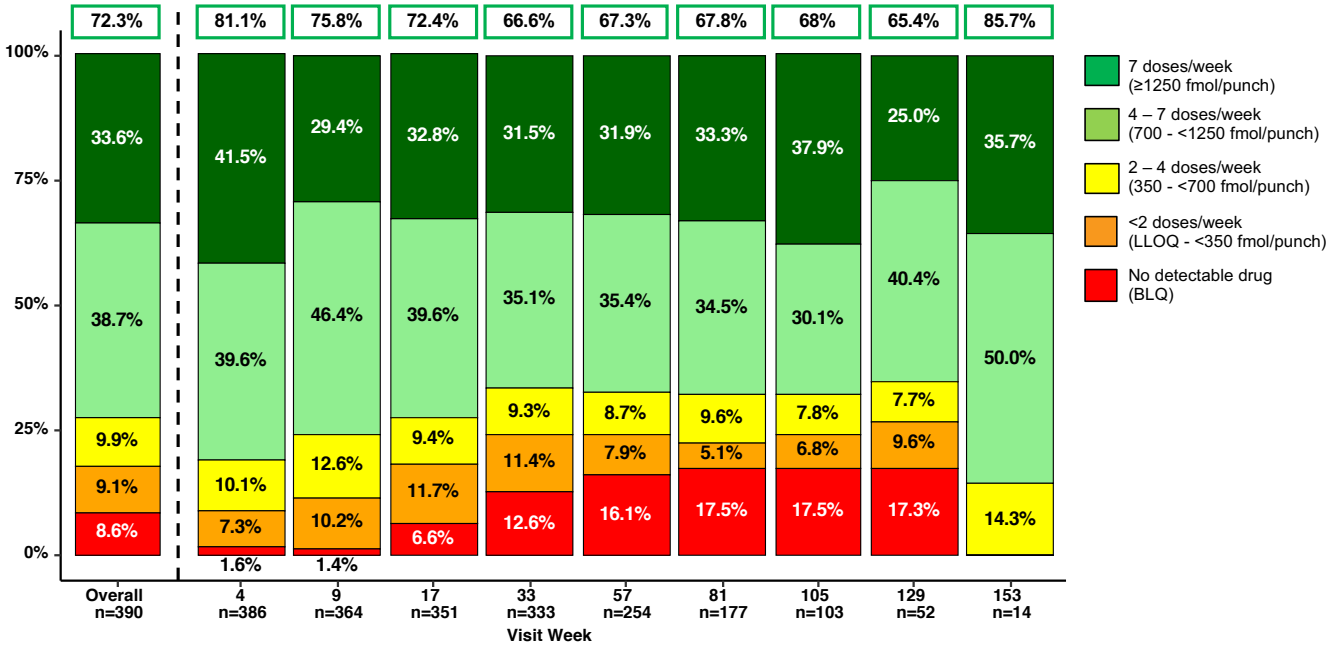
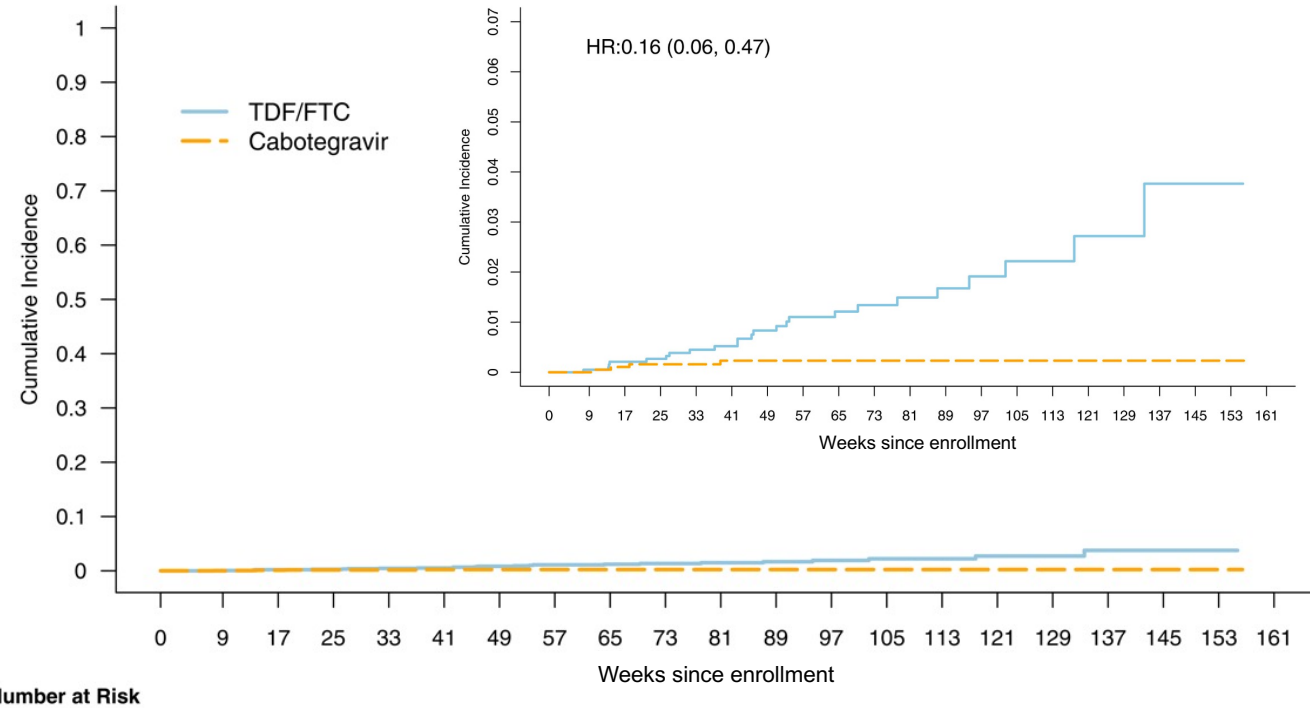
Figure S1. TFV-DP Concentrations by Adherence Category from a Randomly-Selected Subset of Participants Assigned to the TDF/FTC Arm



The figure shows the proportion of a randomly-selected subset of TDF/FTC arm participants with intraerythrocytic tenofovir diphosphate (TFV-DP) concentrations measured in dried blood spots in each adherence category; these data represent average dosing over the previous 1-2 months. The green-boxed numbers above each histogram bar represent the aggregate of 4 or more doses per week; this dosing frequency is anticipated to provide high levels of rectal protection against HIV acquisition. Each participant selected for adherence testing may have up to 8 samples included in this summary. Values for Week 4 were adjusted for days on therapy, since steady state drug concentrations were not yet achieved.

Abbreviations: TVF-DP, tenofovir-diphosphate; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LLOQ, lower limit of quantitation; BLQ, below the limit of quantitation

Figure S2. Per-protocol Kaplan Meier estimates of incident HIV infection



Number at Risk

TDF/FTC	2069	2004	1855	1720	1552	1364	1189	1058	892	748	630	518	398	305	237	182	128	79	49	23	0
Cabotegravir	2109	2021	1853	1706	1537	1366	1186	1050	900	770	633	525	406	301	239	175	136	93	64	20	0

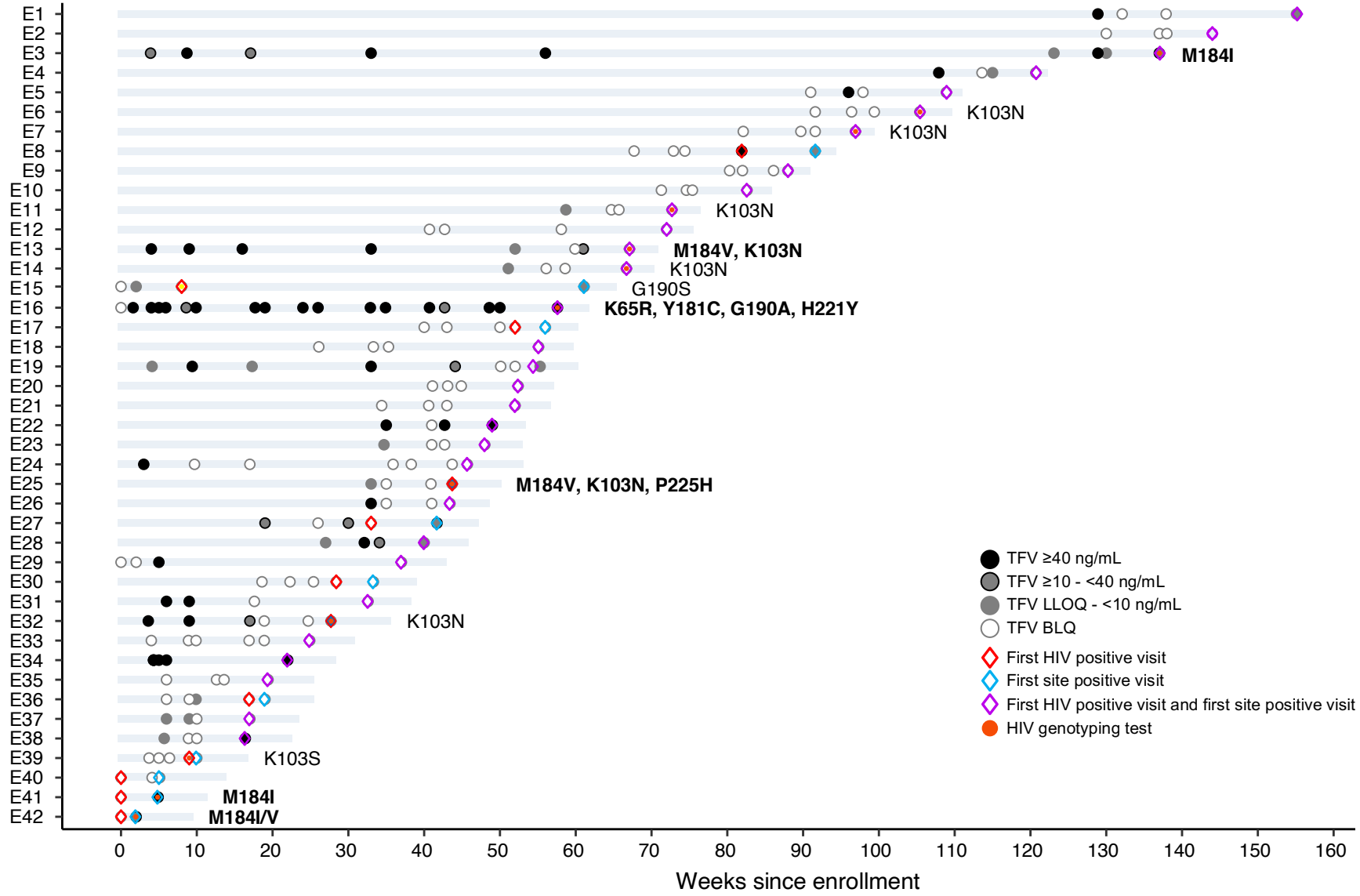
Cumulative Number of Events

TDF/FTC	0	1	4	5	8	9	13	16	17	18	19	20	21	22	22	23	23	24	24	24	0
Cabotegravir	0	0	2	3	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	0

Inclusion in the per-protocol analysis was defined by on-time receipt of blinded injections/dispensation of oral study product during the injection phase. Only participants who initiated injections of CAB-LA were included, and remained in the analysis provided the next injection was not more than 2 weeks after the protocol-scheduled injection date.

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; HR, hazard ratio

Figure S3. Participants with HIV infection in the TDF/FTC arm: TFV concentrations

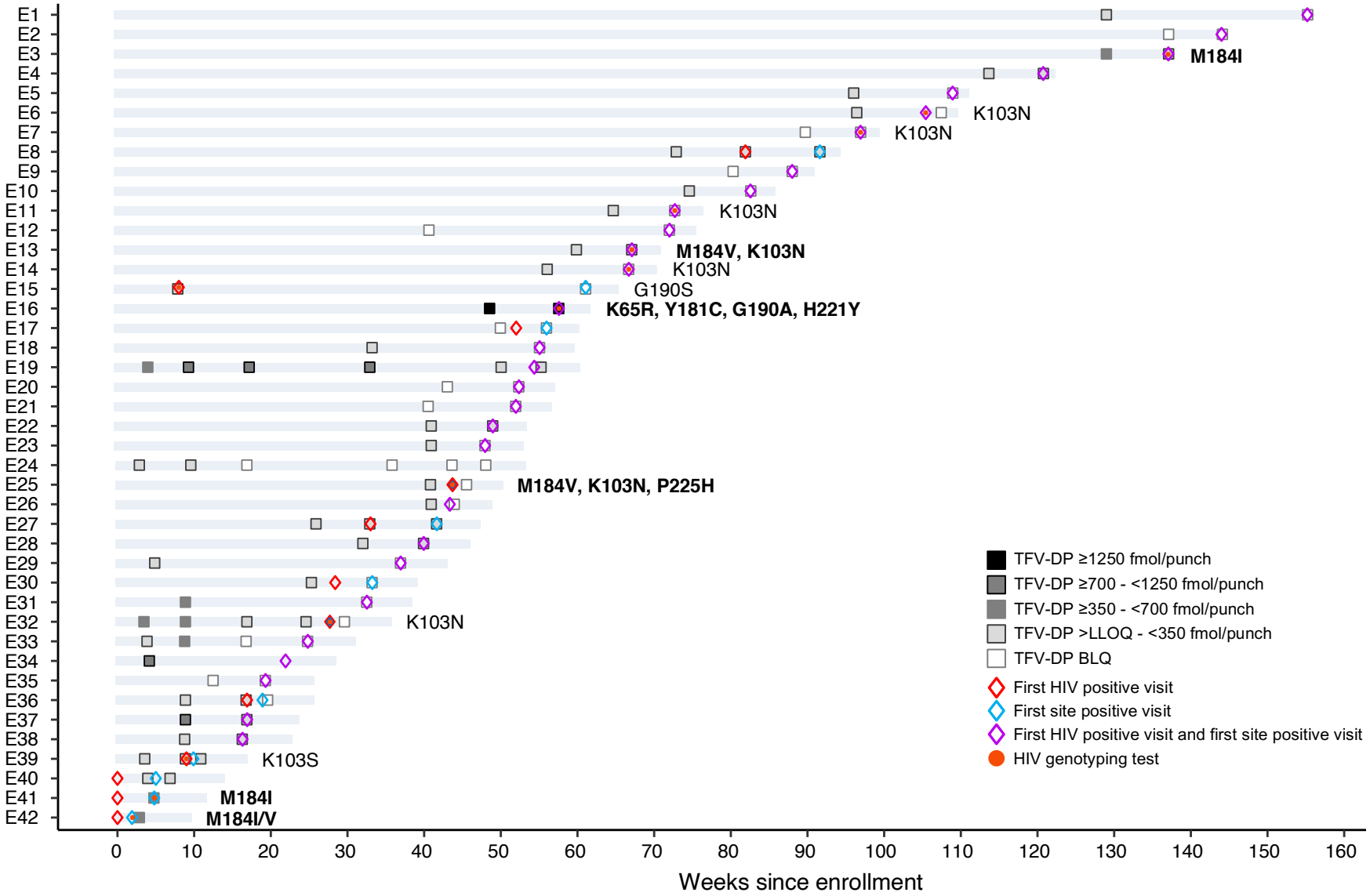


The figures show the timing of key events for participants in the TDF/FTC arm (group E). HIV genotyping results are shown for the first viremic visit (viral load >500 copies/mL). HIV genotyping results are shown to the right of each bar for samples with resistance mutations. These include major mutations that confer resistance to nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs: K65R, M184I/V, M184V) and non-nucleoside reverse transcriptase inhibitors (NNRTIs: K103N, K103S, Y181C, G190A, G190S, H221Y, P225H). Mutations associated with resistance to

TDF/FTC are shown in bold text. Cases without a noted genotype result were WT at first viremic visit, except for E1 and E34 whose genotyping assay failed to amplify.

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; TFV, tenofovir; LLOQ, lower limit of quantitation; BLQ, below the limit of quantitation

Figure S4. Participants with HIV infection in the TDF/FTC arm: TFV-DP concentrations



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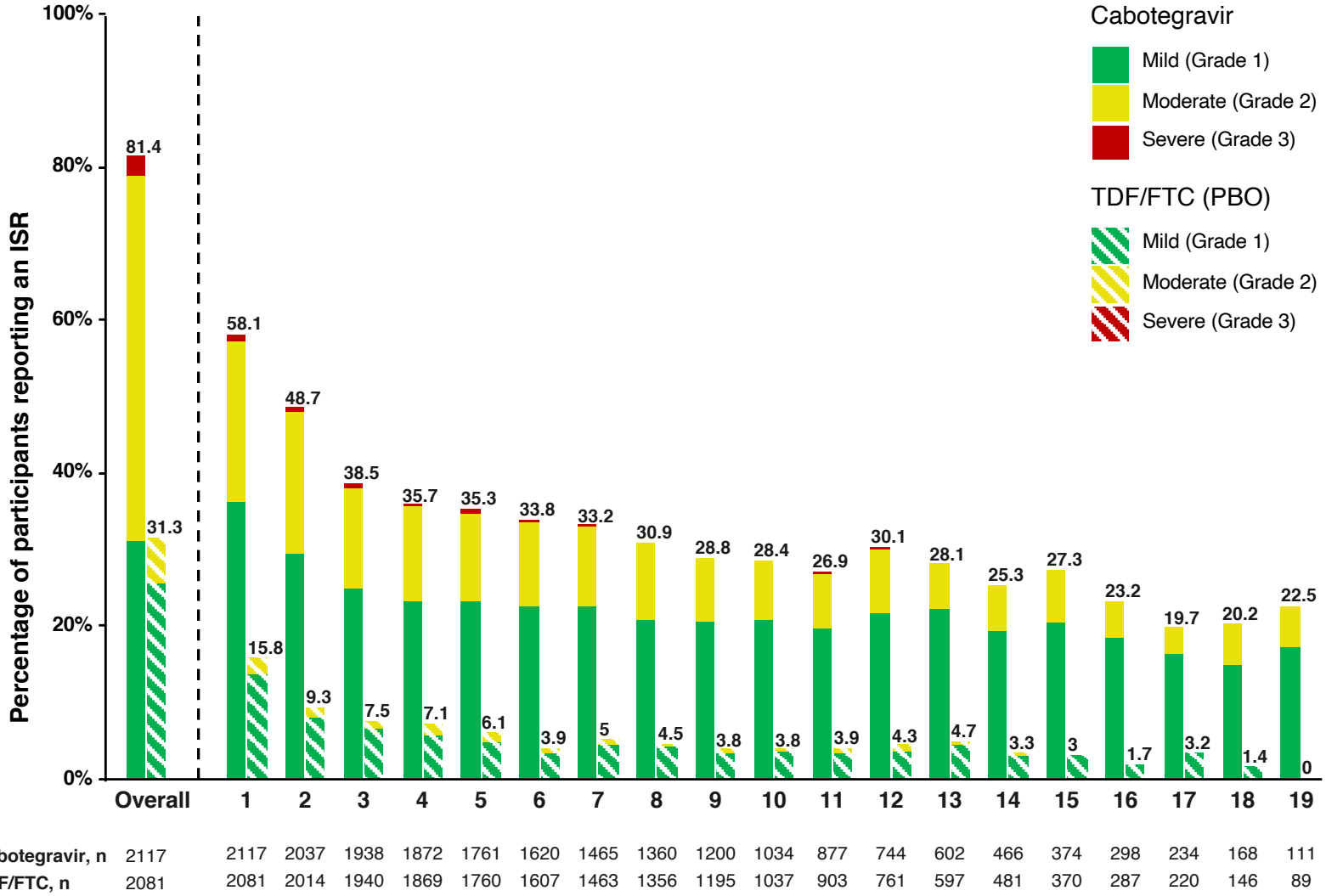
Abbreviations: TVF-DP, tenofovir-diphosphate; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LLOQ, lower limit of quantitation; BLQ, below the limit of quantitation

Figure S5. Injection site reactions over time

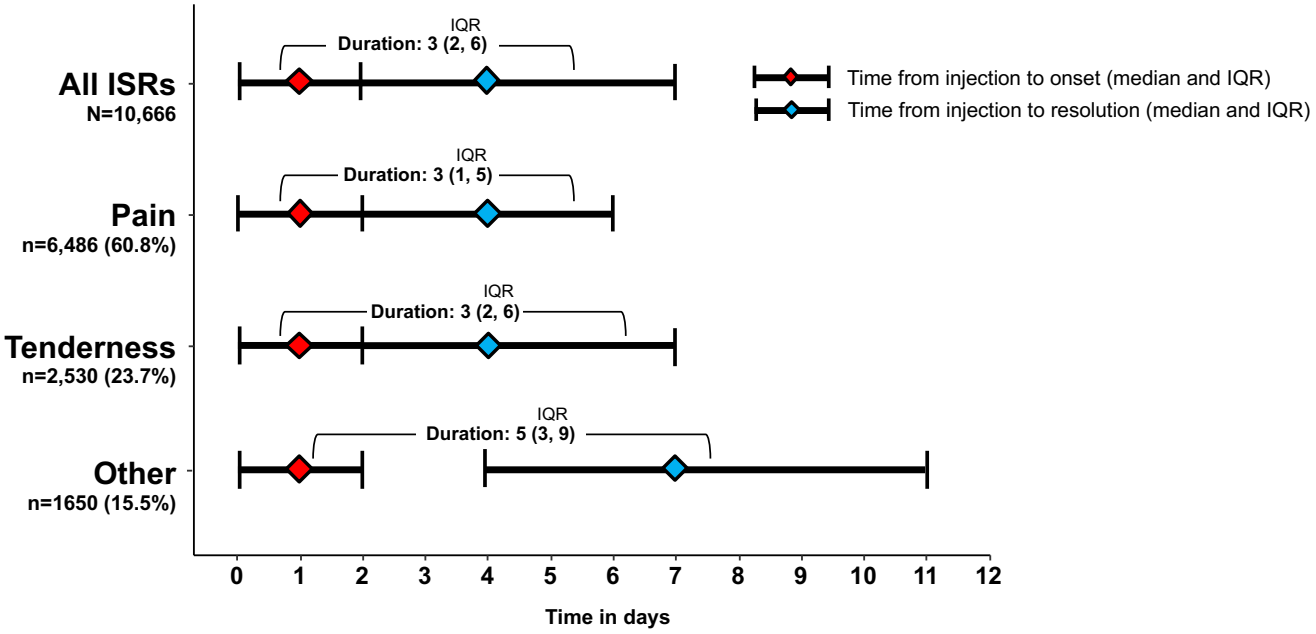


The figure shows the proportion of participants who received at least one injection of blinded study product who reported an injection site reaction. Solid bars represent participants randomized to the cabotegravir arm; hatched bars represent participants randomized to the TDF/FTC arm who

received “placebo” injections composed of a 20% intralipid solution. In each histogram bar, green, yellow and red represent the proportion of reactions that were mild, moderate, and severe, respectively.

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine

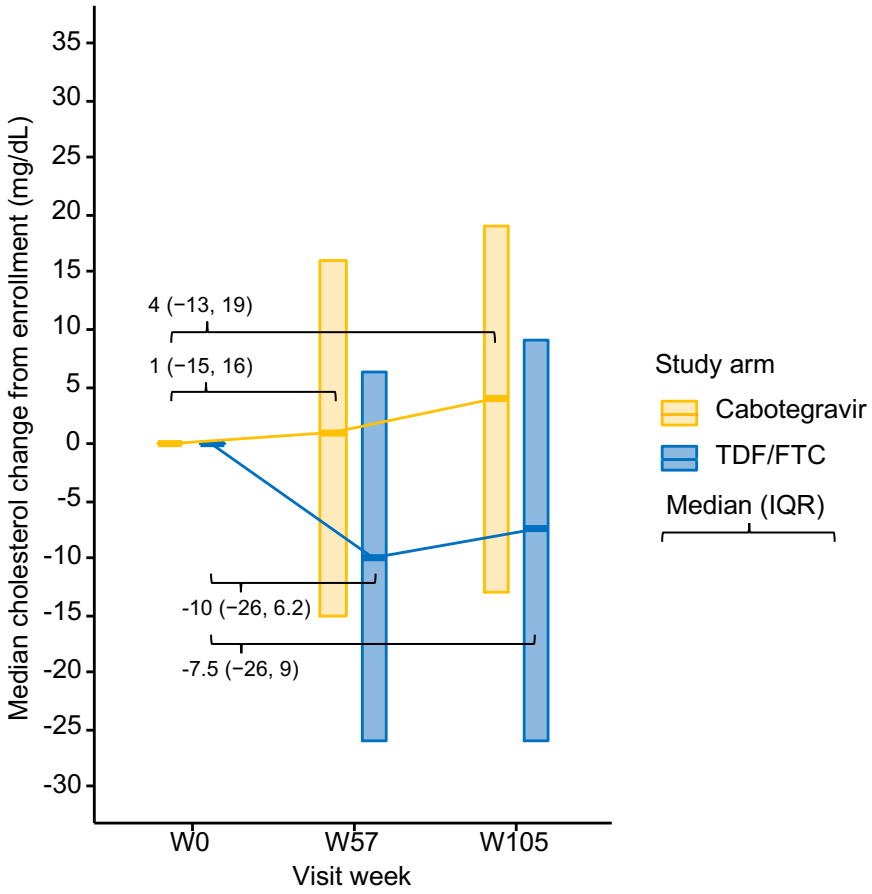
Figure S6. Injection site reactions: timing and duration



The figure shows the timing of onset of ISRs relative to most proximate study product injection. The red diamond represents median time from injection to symptom onset; the blue diamond represents median time from injection to resolution. Error bars represent the IQRs. "Other" reactions include induration, nodule, hematoma, bruising, discoloration, swelling, erythema, itching, warmth, anesthesia, hemorrhage, and abscess.

Abbreviations: ISR, injection site reaction; IQR, interquartile ratios

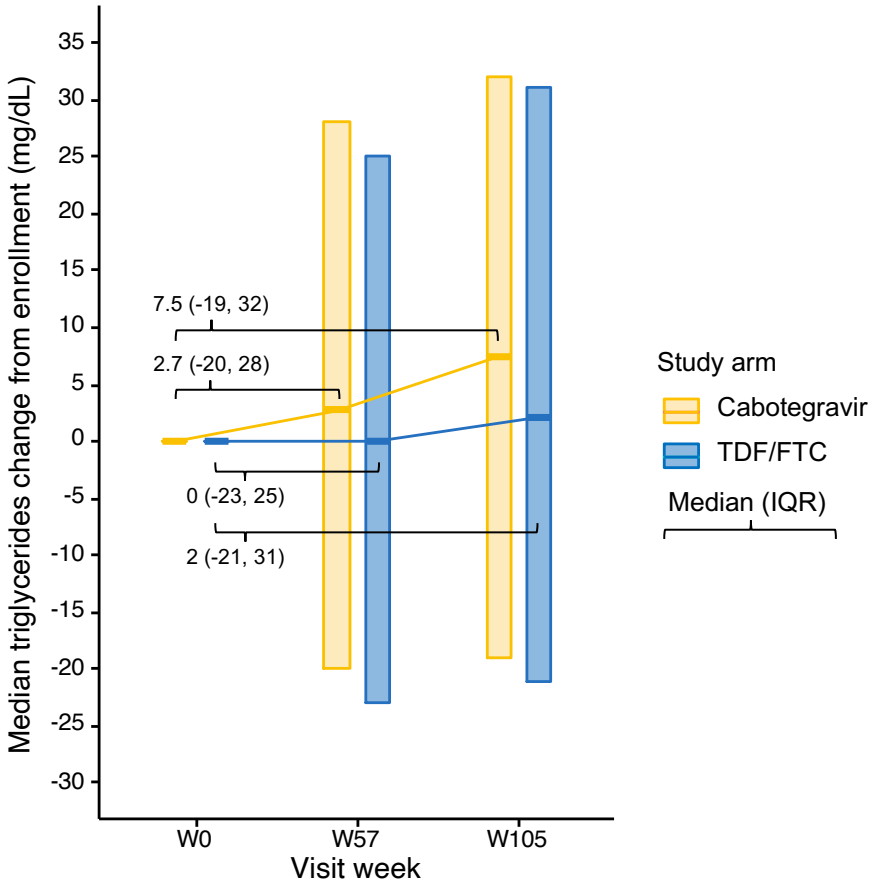
Figure S7 Changes in fasting lipids: Total cholesterol



The figure shows median change in fasting total cholesterol from enrollment to Week 57 and Week 105 by study arm. Bars at Week 57 and Week 105 indicate the median (center horizontal line) and interquartile range (IQR, top and bottom of bars). Brackets represent median change (IQR) from baseline for each study arm.

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC: emtricitabine; IQR, interquartile range.

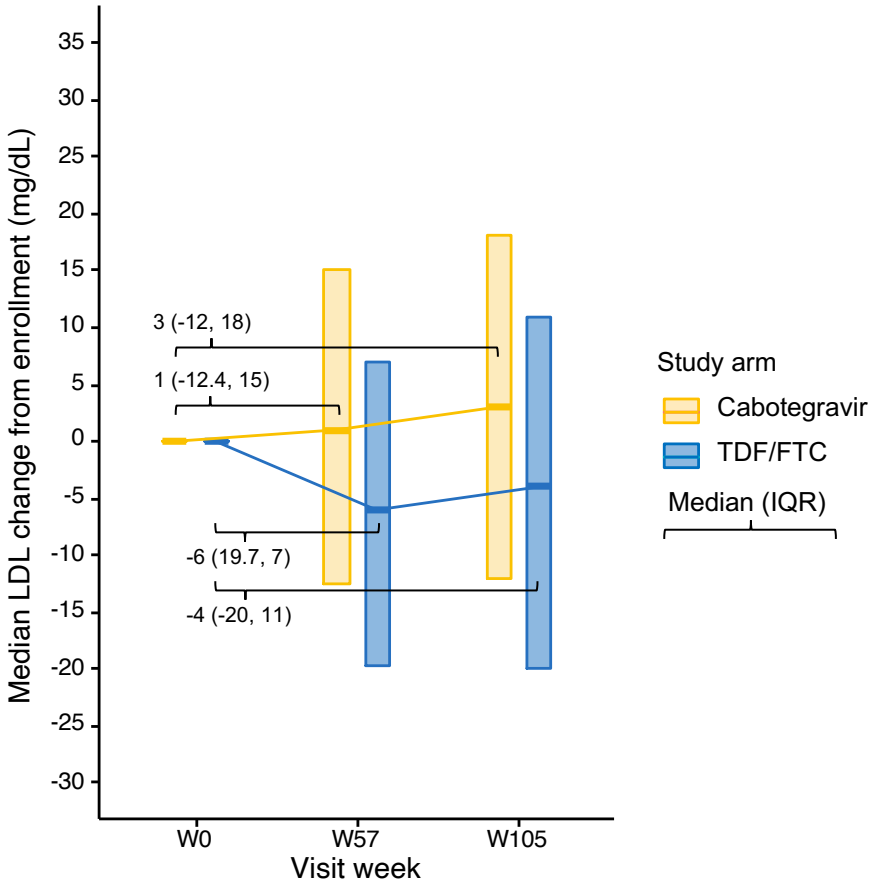
Figure S8. Changes in fasting lipids: Triglycerides



The figure shows median change in fasting triglycerides from enrollment (W0) to Week 57 and Week 105 by study arm. Bars at Week 57 and 105 indicate the median (center horizontal line) and interquartile range (IQR, top and bottom of bars). Brackets represent median change (IQR) from baseline for each study arm.

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC: emtricitabine; IQR, interquartile range.

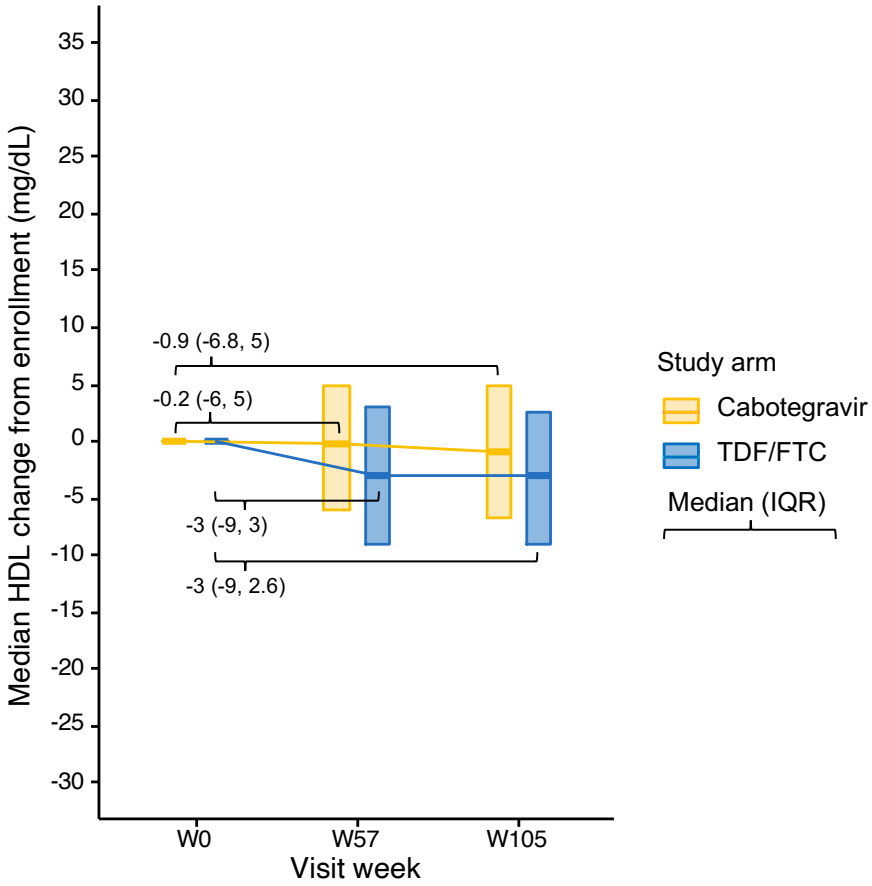
Figure S9. Changes in fasting lipids: Low density lipoprotein (LDL) cholesterol



The figure shows median change in fasting low density lipoprotein (LDL) cholesterol from enrollment (W0) to Week 57 and Week 105 by study arm. Bars at Week 57 and 105 indicate the median (center horizontal line) and interquartile range (IQR, top and bottom of bars). Brackets represent median change (IQR) from baseline for each study arm.

Abbreviations: LDL, low density lipoprotein; TDF, tenofovir disoproxil fumarate; FTC: emtricitabine; IQR, interquartile range.

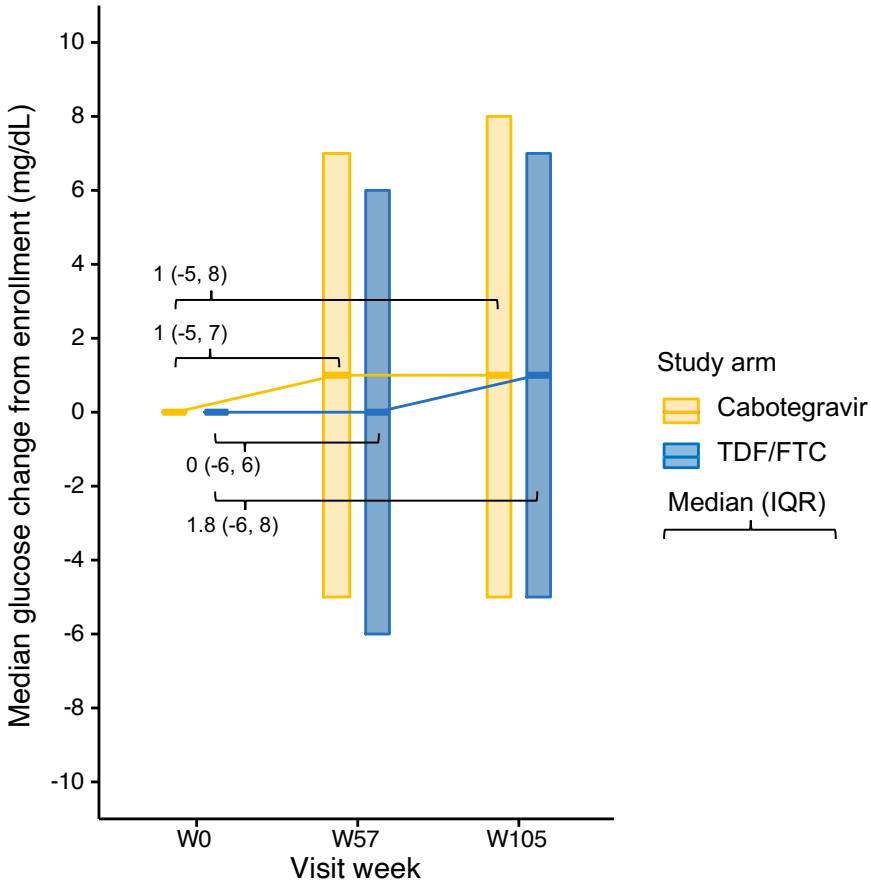
Figure S10. Changes in fasting lipids: High density lipoprotein (HDL) cholesterol



The figure shows median change in fasting HDL cholesterol from enrollment (W0) to Week 57 and Week 105 by study arm. Bars at Week 57 and 105 indicate the median (center horizontal line) and IQR (IQR, top and bottom of bars). Brackets represent median change (IQR) from baseline for each study arm.

Abbreviations: HDL, high density lipoprotein; TDF, tenofovir disoproxil fumarate; FTC: emtricitabine; IQR, interquartile range.

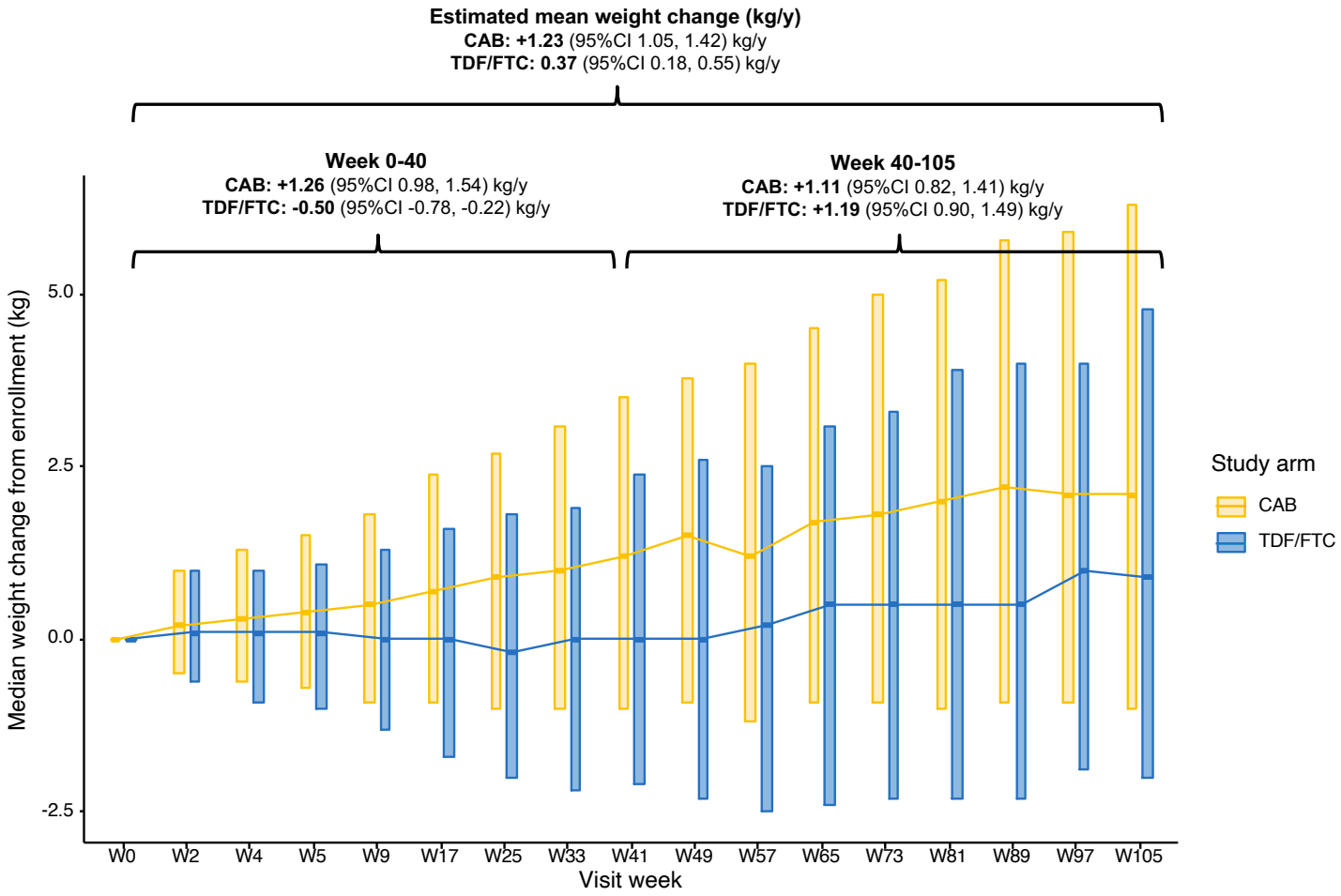
Figure S11. Changes in fasting glucose



The figure shows median change in fasting glucose from enrollment (W0) to Week 57 and Week 105 by study arm. Bars at Week 57 and 105 indicate the median (center horizontal line) and interquartile range (IQR, top and bottom of bars). Brackets represent median change (IQR) from baseline for each study arm.

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC: emtricitabine; IQR, interquartile range.

Figure S12. Median changes in weight (kg) from baseline (W0) to W105



The figure shows median change in weight from enrollment (W0) to Week 105 by study arm. Bars at indicate the median (center horizontal line) and interquartile range (IQR, top and bottom of bars). Linear mixed-effects regression analysis used to determine mean weight change.
Abbreviations: CAB, cabotegravir; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; IQR, interquartile range.

Table S1. Reasons for permanent study product discontinuation by step and arm

	Overall (n=4566)	Cabotegravir (n=2282)	TDF/FTC (n=2284)
Participants who permanently discontinued study product during steps 1 and 2	908 (19.9%)	445 (19.5%)	463 (20.3%)
Participants who permanently discontinued study product during step 1	318 (7.0%)	140 (6.1%)	178 (7.8%)
One or more reactive HIV test results or acute HIV infection suspected	4 (1.3%)	2 (1.4%)	2 (1.1%)
Reported use of prohibited concomitant medication	3 (0.9%)	1 (0.7%)	2 (1.1%)
Participant is unwilling or unable to comply with required study procedures	150 (47.2%)	70 (50.0%)	80 (44.9%)
Participant is currently using or planning to use PrEP or PEP	1 (0.3%)	0 (0.0%)	1 (0.6%)
Low oral adherence*	72 (22.6%)	26 (18.6%)	46 (25.8%)
Clinical AE (protocol mandated)	12 (3.8%)	8 (5.7%)	4 (2.2%)
Laboratory AE (protocol mandated)	13 (4.1%)	6 (4.3%)	7 (3.9%)
CMC recommendation based on a clinical event	4 (1.3%)	1 (0.7%)	3 (1.7%)
CMC recommendation based on a laboratory value	7 (2.2%)	5 (3.6%)	2 (1.1%)
CMC recommendation based on a psychosocial concern	2 (0.6%)	1 (0.7%)	1 (0.6%)
Other	50 (15.7%)	20 (14.3%)	30 (16.9%)
Participants who permanently discontinued study product during step 2	590 (12.9%)	305 (13.4%)	285 (12.5%)
Missing product hold form	42 (7.1%)	20 (6.6%)	22 (7.7%)
One or more reactive HIV test results or acute HIV infection suspected	55 (9.3%)	14 (4.6%)	41 (14.4%)
Reported use of prohibited concomitant medication	9 (1.5%)	4 (1.3%)	5 (1.8%)
Participant is unwilling or unable to comply with required study procedures	197 (33.4%)	100 (32.8%)	97 (34.0%)
Clinical AE (protocol mandated)	23 (3.9%)	11 (3.6%)	12 (4.2%)
Laboratory AE (protocol mandated)	76 (12.9%)	35 (11.5%)	41 (14.4%)
Injection site reaction	23 (3.9%)	23 (7.5%)	0 (0.0%)
CMC recommendation based on a clinical event	6 (1.0%)	3 (1.0%)	3 (1.1%)
CMC recommendation based on a laboratory value	18 (3.1%)	10 (3.3%)	8 (2.8%)
Participant request for injection intolerance (AE or ISR not protocol mandated)	27 (4.6%)	27 (8.9%)	0 (0.0%)
Other	114 (19.3%)	58 (19.0%)	56 (19.6%)

* Defined as <50% of pills taken in step 1

† Includes only adverse events reported by ≥5% of participants in either arm.

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; CMC, Clinical Management Committee; HIV, human immunodeficiency virus; AE, adverse event; ISR, injection site reaction

Table S2. Participant Deaths

No.	Age	Cohort	Arm	Region	Visit	Summary
1	28	MSM	TDF/FTC	Africa	Step 1	Homicide
2	45	MSM	TDF/FTC	Latin America	Step 2, Week 19	Homicide (presumed)
3	26	MSM	TDF/FTC	United States	Step 2, Week 35	Spontaneous intracerebral hemorrhage
4	23	MSM	CAB	Asia	Step 2, Week 17	Suspected methamphetamine overdose
5	34	MSM	CAB	Latin America	Step 2, Week 57	Death due to aspiration of foreign body
6	31	TGW	CAB	Latin America	Step 2, Week 17	Homicide
7	33	MSM	TDF/FTC	Africa	Step 2, Week 9	Traumatic pedestrian accident
8	55	MSM	TDF/FTC	United States	Step 2, Week 73	Complications of myocardial infarction
9	53	MSM	TDF/FTC	Africa	Step 3, Week 24	Homicide
10	35	MSM	TDF/FTC	United States	Step 2, Week 131	Traumatic pedestrian accident
11	19	MSM	CAB	Latin America	Step 2, Week 55	Homicide

Abbreviations: No, number; MSM, men who have sex with men; TGW, transgender women; CAB, cabotegravir; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine

Table S3. Study product discontinuation due to injection site reactions (ISRs) - CAB arm

	Number of Participants	Number Discontinued due to ISR	Percentage discontinued due to ISRs	95% CI
Overall	2117	50	2.4%	(1.7%, 3.0%)
Maximum grade ISR reported				
None	393	0	0.0%	(0.0%, 0.0%)
Grade 1	715	1	0.1%	(-0.1%, 0.4%)
Grade 2	955	26	2.7%	(1.7%, 3.8%)
Grade 3	54	23	42.6%	(29.4%, 55.8%)

Abbreviations: CAB, cabotegravir; ISR: CI, confidence intervals

Table S4. Baseline sexually transmitted infections

	Overall	Cabotegravir	TDF-FTC
Enrolled participants*	4566	2282	2284
Syphilis			
Tested – no. (%)	4556 (99.8)	2277 (99.8)	2279 (99.8)
Diagnosed with active syphilis – no. (%)	237 (5.2)	122 (5.4)	115 (5)
Gonorrhea (urine)			
Tested – no. (%)	4561 (99.9)	2281 (>99.9)	2280 (99.8)
Positive – no. (%)	31 (0.7)	13 (0.6)	18 (0.8)
Gonorrhea (rectal)			
Tested – no. (%)	4561 (99.9)	2281 (>99.9)	2280 (99.8)
Positive – no. (%)	298 (6.5)	148 (6.5)	150 (6.6)
Chlamydia (urine)			
Tested – no. (%)	4561 (99.9)	2281 (>99.9)	2280 (99.8)
Positive – no. (%)	123 (2.7)	66 (2.9)	57 (2.5)
Chlamydia (rectal)			
Tested – no. (%)	4561 (99.9)	2281 (>99.9)	2280 (99.8)
Positive – no. (%)	505 (11.1)	248 (10.9)	257 (11.3)
Hepatitis B virus			
Tested – no. (%)	4562 (99.9)	2280 (99.9)	2282 (99.9)
Non-immune (HBsAb-/HBcAb-)	1729 (37.9)	872 (38.2)	857 (37.6)
Vaccine induced immunity (HBsAb+/HBcAb-)	2304 (50.5)	1164 (51.1)	1140 (50)
Isolated HBcAb+	64 (1.4)	29 (1.3)	35 (1.5)
Natural immunity (HBsAb+/HBcAb+)	422 (9.3)	193 (8.5)	229 (10)
Other	43 (0.9)	22 (1.0)	21 (0.9)

*Inappropriately enrolled participants and participants with invalid identification numbers due to duplicate screening or enrollment are excluded.
Participants with detected hepatitis B surface antigen (HBsAg) at screening were excluded from enrollment. Participants without immunity to hepatitis B Virus were referred for vaccination according to local standards of care.
Abbreviations: TDF, tenofovir disoproxil fumarate; FTC: emtricitabine; HBsAb, hepatitis B surface antibody; HBcAb, hepatitis B core antibody

Table S5. Incident sexually transmitted infections

	Overall	Cabotegravir	TDF-FTC
Enrolled participants*	4566	2282	2284
Syphilis			
Person years – no.	5531	2776	2755
Rate per 100 person-years†	16.7	16.6	16.7
Gonorrhea (urine)			
Person years – no.	5464	2746	2718
Rate per 100 person-years†	2.45	2.77	2.13
Gonorrhea (rectal)			
Person years – no.	5434	2725	2709
Rate per 100 person-years†	11	11.1	11
Chlamydia (urine)			
Person years – no.	5463	2745	2718
Rate per 100 person-years†	4.56	4.44	4.67
Chlamydia (rectal)			
Person years – no.	5435	2725	2710
Rate per 100 person-years†	16.8	15.8	17.8
Hepatitis C virus			
Person years – no.	4105	2050	2056
Rate per 100 person-years†	0.54	0.49	0.58

*Inappropriately enrolled participants and participants with invalid identification numbers due to duplicate screening or enrollment are excluded.
†Person-years are calculated from enrollment to the latest visit with a test result (either positive or negative).
Note: Testing for bacterial sexually transmitted infections was performed every six months after enrollment. This summary also includes STI tests that were not planned but were performed by sites due to suspected infections. For the bacterial STI's, the same participant can be infected more than once. Although we did not assess HBV systematically, there were eight reported cases of acute HBV during the primary analysis period. Three of these cases occurred in participants randomized to the TDF/FTC arm; five occurred participants randomized to the CAB arm.
Abbreviations: no, number; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; STI, sexually transmitted infection; HBV, Hepatitis B virus; CAB, cabotegravir.

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