Integrated Review

Table 1. Administrative Application Information, NDA 215499

Category	Application Information
Application type	NDA
Application number(s)	215499
Priority or standard	Priority
Submit date(s)	7/23/2021
Received date(s)	7/23/2021
PDUFA goal date	1/23/2022
Division/office	Division of Antivirals (DAV)
Review completion date	12/16/2021
Established/proper name	Cabotegravir extended-release injectable suspension
(Proposed) proprietary name	APRETUDE
Pharmacologic class	Integrase strand transfer inhibitor [INSTI]
Code name	Cabotegravir: CAB, GSK1265744
Applicant	ViiV Healthcare
Dosage form(s)/formulation(s)	Injectable suspension
Dosing regimen	Initiate injections of APRETUDE 600 mg (3 mL) on final day of oral lead-in with a single APRETUDE 600 mg (3 mL) injection at two time points 4 weeks apart and continue with injections of APRETUDE 600 mg (3 mL) every 8 weeks thereafter
Applicant proposed indication(s)/ population(s)	Pre-exposure prophylaxis (PrEP) of HIV-1 infection in adults and adolescents
Proposed SNOMED indication	40780007 |Human immunodeficiency virus type I (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	Initiate APRETUDE with a single 600 mg (3-mL) injection given 1 month apart for 2 consecutive months on the last day of an oral lead-in if used or within 3 days and continue with the injections every 2 months thereafter
Approved indication(s)/ population(s) (if applicable)	APRETUDE is indicated in at-risk adults and adolescents weighing at least 35 kg for pre exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test prior to initiating APRETUDE (with or without an oral lead-in with oral cabotegravir) for HIV-1 PrEP
Approved SNOMED term for indication (if applicable)	40780007: Human immunodeficiency virus 1 infection (disorder)

Table 2. Administrative Application Information, NDA 212887

Category	Application Information
Application type	Efficacy Supplement
Application number(s)	212887
Priority or standard	Priority
Submit date(s)	7/23/2021
Received date(s)	7/23/2021
PDUFA goal date	12/10/2021
Division/office	Division of Antivirals (DAV)
Review completion date	12/16/2021
Established/proper name	Cabotegravir Tablets
Proprietary name	VOCABRIA
Pharmacologic class	Integrase strand transfer inhibitor [INSTI]
Code name	Cabotegravir: CAB, GSK1265744
Applicant	ViiV Healthcare
Dosage form(s)/formulation(s)	Tablet
Dosing regimen	30 mg of cabotegravir taken orally once daily for approximately one month prior to the initiation of APRETUDE to assess tolerability of cabotegravir
Applicant proposed indication(s)/ population(s)	Pre-exposure prophylaxis (PrEP) of HIV-1 infection in adults and adolescents
Proposed SNOMED indication	40780007 |Human immunodeficiency virus type I (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	Oral lead-in may be used to assess the tolerability of cabotegravir prior to the initiation of APRETUDE. The recommended oral daily dose is one 30-mg tablet of VOCABRIA for approximately 1 month (at least 28 days). Following oral lead-in, start initiation injection of APRETUDE on the last day of oral lead-in or within 3 days.
Approved indication(s)/ population(s) (if applicable)	VOCABRIA is indicated in at-risk adults and adolescents weighing at least 35 kg for short-term pre exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test prior to initiating VOCABRIA for HIV-1 PrEP. VOCABRIA may be used as: • oral lead-in to assess the tolerability of cabotegravir prior to administration of APRETUDE (cabotegravir extended-release injectable suspension). • oral PrEP for patients who will miss planned injection dosing with APRETUDE
Approved SNOMED term for indication (if applicable)	40780007: Human immunodeficiency virus 1 infection (disorder)

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Glossary

3TC	lamivudine
Ab	antibody
ADAE	adverse event analysis dataset
ADDS	adverse event in the disposition dataset
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
Ag	antigen
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
BIC	bictegravir
BMD	bone mineral density
BMI	body mass index
CAB	cabotegravir
CDS	clinical data scientist
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatinine kinase
C_{max}	maximum plasma concentration
CMC	clinical management committee
CPK	creatine phosphokinase
CSR	clinical study report
CVA	cerebrovascular accident
DAIDS	Division of Acquired Immunodeficiency Syndrome
DBS	dried blood spot
DMPA	depot medroxyprogesterone acetate
DRVr	darunavir/ritonavir
DSMB	Data Safety Monitoring Board
DTG	dolutegravir
DTI	direct to injection
DXA	dual x-ray absorptiometry
EAC	Endpoint Adjudication Committee
EFV	efavirenz
EVG	elvitegravir
FDA	Food and Drug Administration
FMQ	FDA Medical Dictionary for Regulatory Activities query
FTC	emtricitabine
GSK	GlaxoSmithKline
HDL	high-density lipoprotein
HR	hazard ratio
HSR	hypersensitivity reaction

HSV-2	herpes simplex virus-2
IDU	injection drug use
IM	intramuscular
IND	investigational new drug
INSTI	integrase strand transfer inhibitor
IQR	interquartile range
ISR	injection site reactions
LA	long-acting
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MSM	men who have sex with men
NET-EN	norethisterone enanthate
NI	noninferiority
NDA	new drug application
OBSP	on blinded study product
OLI	oral lead-in
OLT	open-label emtricitabine/tenofovir
PA-IC_{90}	protein-adjusted 90% inhibitory concentration
PK	pharmacokinetic
PMR	postmarketing requirement
PrEP	pre-exposure prophylaxis
PT	preferred term
PY	person-year(s)
Q4W	every 4 weeks
Q8W	every 8 weeks
RAL	raltegravir
RAS	resistance associated substitution
RSC	Regulatory Support Center
RPV	rilpivirine
RR	risk ratio
RRL	lower bound of the 95% CI of the risk ratio
SAE	serious adverse event
SAP	statistical analysis plan
SMSQ	Study Medication Satisfaction Questionnaire
SOC	system organ class
SOE	schedule of evaluations
SSP	Study Specific Procedures
STI	sexually transmitted infection
SUR	safety update report
TAF	tenofovir alafenamide
TFV-DP	tenofovir diphosphate
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
TGW	transgender women
VOICE	Vaginal and Oral Interventions to Control the Epidemic

ULN upper limit of normal

APPEARS THIS WAY ON ORIGINAL

I. Executive Summary

1. Summary of Regulatory Action

The new drug application (NDA) for APRETUDE, an extended-release injectable form of cabotegravir (CAB), and supplemental NDA (sNDA) for VOCABRIA, an oral formulation of CAB, were submitted by ViiV Healthcare. These NDAs were reviewed by the multidisciplinary review team.

CAB is a previously approved integrase strand transfer inhibitor (INSTI). CABENUVA, an extended-release, injectable, two-drug copackaged product containing CAB and rilpivirine (RPV), is approved as a complete regimen for the treatment of HIV-1 infection in adults and replaces the current antiretroviral (ARV) regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL (c/mL)) on a stable regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV. VOCABRIA is approved for use in combination with RPV for short-term treatment to HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 c/mL) on a stable regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV. VOCABRIA is indicated for use as 1) an oral lead-in (OLI) to assess the tolerability of CAB prior to administration of CABENUVA, and 2) an oral therapy (up to 2 consecutive months) for patients who will miss planned dosing with CABENUVA injectable suspensions.

The intended indication for APRETUDE is for use as a pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in at-risk adults and adolescents weighing at least 35 kg. APRETUDE is administered by a healthcare provider every 8 weeks (Q8W). The expanded indication for VOCABRIA includes use as a short-term PrEP to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg. VOCABRIA may be used as:

- An OLI to assess the tolerability of CAB prior to administration of APRETUDE (CAB extended-release injectable suspension for HIV-1 PrEP)
- An oral therapy for patients who will miss planned injection dosing with APRETUDE for HIV-1 PrEP

All data reviewed under the APRETUDE NDA support label revisions for VOCABRIA. Please refer to Section 21 for a summary of changes to VOCABRIA label and for a summary of the data to support the optional OLI.

Each discipline (clinical, virology, clinical pharmacology, pharmacology/toxicology, statistics, chemistry and manufacturing and regulatory) did not identify any issues that preclude approval for NDA 215449 or sNDA 212887. I, the signatory authority, agree the benefit-risk assessment favors approval.

ViiV submitted two adequate and well-controlled phase 3 trials that provided substantial evidence of efficacy for the indications approved. Trial HPTN 083 was conducted in cisgender

men and transgender women who have sex with men, and Trial HPTN 084 was conducted in cisgender women. No significant issues relevant to the benefit of CAB for PrEP were identified during the review. The submitted data provide substantial evidence of CAB efficacy to reduce the risk of HIV-1 infection in men who have sex with men, transgender women, and cisgender women. Both trials demonstrated CAB is superior to TRUVADA (tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)). A 66% and 88% reduction in the risk of HIV-1 infection was seen in Trials HPTN 083 and HPTN 084, respectively.

The safety evaluation for APRETUDE was adequate, and the demonstrated safety profile for PrEP to reduce the risk of sexually acquired HIV-1 infection is acceptable for the indicated dose and population. No new or unexpected safety findings were noted, and the safety profile was consistent with the safety profile observed with CABENUVA. Local and systemic injection site reactions (ISRs) were common.

The use of oral CAB as a 4-week OLI was adequate to assess the tolerability of CAB prior to receiving CAB injections. ViiV submitted data from the FLAIR trial in subjects with HIV-1 infection to support an optional OLI with oral CAB prior to the initiation of APRETUDE to assess the tolerability of CAB. Notably, no safety and efficacy data are available for use of APRETUDE without an OLI. However, in the FLAIR trial involving subjects with HIV-1 infection, the data showed that an oral CAB lead-in is not needed to ensure adequate plasma CAB exposure upon initiation of injections and that the safety and efficacy results of CABENUVA were similar when administered with and without an OLI (see Section 7.7.2 for details). Therefore, the review team supports the optional oral CAB lead-in dosing. Healthcare providers and individuals can decide to use an oral CAB lead-in or proceed directly to injection of APRETUDE without the use of an oral CAB lead-in.

The long-acting properties of APRETUDE have potential advantages and disadvantages. The extended-release injectable formulations eliminate the need for adherence to oral daily medications and can be administered Q8W. However, because residual concentrations of CAB remain for prolonged periods (12 months or longer), careful selection of patients who agree to the required every-2-month injection dosing schedule is imperative. Nonadherence to the every-2-month injections or missed injections can lead to HIV-1 acquisition and development of resistance to CAB or to the INSTI drug class.

An important review issue was the risk of prolonged exposure to CAB monotherapy in those unaware of being infected by HIV-1, including pharmacologic failures, which can be attributed to a delay in HIV-1 diagnosis. A delay in HIV-1 diagnosis may be due to CAB's ability to suppress viral replication, albeit for a limited to moderate period of time. A delay in HIV-1 diagnosis could subsequently result in the development of resistance to CAB and to other INSTIs, which are important considerations for ARV treatment options. Individuals with a delay in HIV-1 diagnosis are at risk of transmitting HIV-1—and perhaps INSTI-resistant variants—to sexual partners. Overall, the benefit-risk assessment is favorable for CAB despite these concerns. Additional risk-mitigation strategies with regards to testing are prominently displayed in Sections 2 and 5 of product labeling. The potential for a delayed HIV-1 diagnosis necessitates more stringent testing recommendations. Based on the available data, the review team determined frequent testing for HIV-1 infection is needed prior to initiating treatment with APRETUDE or oral CAB (optional 4-week lead-in) and with each subsequent injection of APRETUDE, using RNA-specific assays approved or cleared by FDA for the diagnosis of acute or primary HIV-1 infection. If an antigen/antibody-specific test is used, negative results should

be confirmed using an RNA-specific assay. Additionally, the review team recommended a postmarketing requirement to collect additional data on pharmacologic failures and resistance via a 5-year observational post marketing study.

For detailed information supporting the basis for the benefit-risk assessment, please refer to the details in this integrated assessment document.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 3. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HIV-1 infection affects more than 37 million people globally and an estimated 1.2 million adults and adolescents in the United States. • There is no cure for HIV-1 infection. Once infection is established, it is a life-long condition that requires chronic therapy with antiretroviral drug regimens to manage. If left untreated, it can lead to acquired immunodeficiency syndrome (AIDS), which is associated with significant morbidity and mortality, and increased risk of transmission to others, a major public health concern.	HIV-1 is a serious and life-threatening disease that affects a large population.
Current Treatment Options	• TRUVADA® (tenofovir disoproxil fumarate (TDF) 300 mg /emtricitabine (FTC) 200 mg) is approved for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 sexual acquisition in at-risk adults and adolescents weighing at least 35 kg. This indication includes both men and women at risk. – The dosing regimen for TDF/FTC for PrEP is one tablet by mouth once daily. – The TDF component of TDF/FTC has been associated with bone loss and renal toxicity, including proximal renal tubulopathy, which occurs in less than 1% of individuals using TDF/FTC for treatment or prevention. • DESCOVY® (FTC 200 mg/tenofovir alafenamide (TAF) 25 mg) is approved for at-risk adults and adolescents weighing at least 35 kg for PrEP to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. – The dosing regimen for FTC/TAF for PrEP is one tablet by mouth once daily.	New drug products that are as effective as the currently approved PrEP options but which are not dependent on daily adherance to an oral medication are needed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	– TAF does not appear to impact renal function and bone mineral density parameters to the degree that TDF does. • According to the Centers for Disease Control and Prevention (CDC), currently available HIV-1 PrEP options reduce the risk of getting HIV-1 from sex by about 99% when taken as prescribed. Efficacy is strongly correlated with adherence to the daily dosing PrEP regimen. • In 2019, approximately 23% of the U.S. population eligible for pre-exposure prophylaxis (PrEP) were prescribed it.[1]	
Benefit	• APRETUDE is an extended-release injectable suspension of the integrase strand transfer inhibitor (INSTI) cabotegravir (CAB LA). It is administered by intramuscular injection every 4 weeks for the first two doses, and every 8 weeks thereafter. • The efficacy of CAB LA for PrEP was established in two randomized, double-blind, active-controlled trials, HPTN 083 and HPTN 084. • In Trial HPTN 083, 4,566 cisgender men and transgender women who have sex with men were randomized 1:1 and received either CAB or TDF/FTC up to Week 153. The primary endpoint was the rate of incident HIV-1 infections. At the time of the first interim analysis (May 2020), there were 52 adjudicated HIV-1 injections (13 in the CAB arm and 39 in the TDF/FTC arm). The primary analysis demonstrated the superiority of CAB compared with TDF/FTC with a 66% reduction in the risk of acquiring HIV-1 infection, hazard ratio (95% CI) 0.34 (0.18, 0.61). At that time, the blinded portion of the trial was stopped for efficacy. • In Trial HPTN 084, 3,224 cisgender women were randomized 1:1 and received either CAB or TDF/FTC up to Week 153, and the primary endpoint was the same as that for HPTN 083. At the second interim analysis (November 2020), there were 40 adjudicated HIV-1 injections (4 in the CAB arm and 36 in the TDF/FTC arm). The primary	The submitted clinical data provide substantial evidence of CAB LA efficacy to reduce the risk of HIV-1 acquisition among men who have sex with men, transgender women, and cisgender women. The data indicate that CAB LA is superior to approved TDF/FTC. Not only does CAB LA provide superior efficacy over the currently approved HIV-1 PrEP option, TDF/FTC, but it provides an option for HIV-1 PrEP that does not require daily oral administration and is not dependent on high daily adherance for efficacy, Based on the same routes of HIV-1 transmission and similar drug exposures between adults and adolescents, the submitted adult efficacy data for CAB can be extrapolated to support a PrEP indication in at-risk adolescents as well.

[1] https://www.cdc.gov/nchhstp/newsroom/2021/2019-national-hiv-surveillance-system-reports.html

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	analysis demonstrated the superiority of CAB compared with TDF/FTC with an 88% reduction in the risk of acquiring HIV-1 infection, hazard ratio (95% CI) 0.12 (0.05, 0.31). At that time, the blinded portion of the trial was stopped for efficacy. • In both trials, efficacy of CAB for PrEP was consistent across various subgroups defined by age, race, region, or other baseline factors, although some of these comparisons were limited by subgroup sample size. • The safety and efficacy of CAB for HIV-1 PrEP in HIV-1 uninfected adolescents are supported by the safety and PK of CAB in HIV-1 uninfected adults in HPTN 083 and HPTN 084 as well as in HIV-1-infected adolescents in the MOCHA study. No clinically relevant difference in CAB exposure was observed between participants aged 12 to <18 years in the MOCHA study and adult participants from the CAB treatment program. Therefore, the efficacy of CAB can be extrapolated to support a PrEP indication in at-risk adolescents.	
Risk and Risk Management	<u>Safety and Tolerability</u> • The safety database for CAB LA for HIV-1 PrEP was considered adequate. The most common adverse drug reactions (reported in ≥3% of CAB subjects in either HPTN 083 or HPTN 084) were injection site reactions, diarrhea, headache, pyrexia, fatigue, nausea, dizziness, and upper respiratory tract infections. • The potentially serious AEs depressive disorders, hypersensitivity reactions, and hepatotoxicity are adequately labeled under WARNINGS and PRECAUTIONS. These events are reported with other INSTIs. • In both HPTN 083 and HPTN 084, participants in the CAB arm experienced greater weight gain than those in the TDF/FTC arm. In HPTN 083, an on-treatment weight increase of ≥10% from baseline was reported in 15.7% and 10.6% of CAB and TDF/FTC participants, respectively. In HPTN 084, 28.4% and 23.5% of CAB and TDF/FTC	Overall, the safety data are adequate to assess the safety of CAB LA for the proposed indication, dosage regimen, duration, and patient populations. The overall safety profile of CAB LA is generally similar to that of other INSTIs, with the addition of frequent Grade 1 and 2 injection site reactions. Common adverse drug reactions, weight gain, and serious drug reactions will be conveyed through labeling. Despite the rare occurrence of pharmacologic failures as well as delays in HIV-1 diagnosis by many HIV-1 diagnostic assays that may increase individuals' risk for the development of INSTI resistance, the benefit-risk assessment for CAB LA for HIV-1 PrEP remains highly favorable. The overall rate of HIV-1 infections in HPTN 083 and HPTN 084 was very low, even when compared to F/TDF, an approved PrEP product that is known to be highly efficacious when used as recommended. However, the implementation of more stringent testing algorithms than what has been recommended for currently

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	participants, respectively, experienced weight increase of ≥10% from baseline. Weight gain has been reported in association with the use of other INSTIs. In addition, CAB participants in both trials also experienced a very modest increase in triglyceride levels between baseline and Month 15. <u>Risk of Prolonged Exposures to CAB Monotherapy in Subjects who Become HIV-1 Infected</u> • Currently approved HIV-1 PrEP options are highly effective when taken daily as prescribed. CAB LA provides a PrEP option that does not depend on daily adherence to be effective. However, among the 20 HIV-1 infections identified in participants receiving CAB in HPTN 083 and HPTN 084, there were 6 subjects in HPTN 083, and no subjects in HPTN 084, who were diagnosed with HIV-1 infection despite having achieved "adequate" drug concentrations during the OLI or despite on-time injections in Step 2 (to be referred to as "pharmacologic failures").[2] Among these 6 participants, 4 participants became infected despite receiving scheduled CAB LA injections and 2 became infected during the OLI despite having achieved target plasma CAB concentrations. Examination of various characteristics (e.g., body mass index (BMI), region, history of injection drug use, and report of sexually transmitted infections) of the 6 HPTN 083 participants who experienced pharmacologic failure did not reveal any clear trends or etiologies for pharmacologic failure. • Among HIV-1-infected individuals using an ARV-based PrEP product, the ability of HIV-1 diagnostic assays to detect infection may be affected, leading to a delay in HIV-1 diagnosis. This is thought to be due to a reduction of the	approved PrEP products is warranted. Specifically, HIV-1 testing should be conducted using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection prior to initiating CAB for HIV-PrEP and prior to each CAB LA injection. This recommendation will be conveyed through product labeling, including through a BOX WARNING. Further, to better understand the risk of pharmacologic failure, delayed HIV-1 diagnosis, and the development of INSTI resistance, the Applicant has proposed a 5-year observation postapproval study to be conducted as a postmarketing requirement. Both the OLI and DTI approaches are considered acceptable from a safety and efficacy perspective, and both will be described in Section 2 of the APRETUDE label. For patients who find daily medication adherence challenging, a DTI approach may be preferable. For other patients with concerns regarding tolerability and adverse reactions, an OLI approach may be preferable. The decision to start with an OLI or to go directly to injections should be left to the discretion of the patient and the healthcare provider.

[2] Adequate plasma drug concentrations are defined as ≥0.65 mcg/mL ≥1.6μM), which are equal to or greater than four times the protein-adjusted 90% effective concentration (4x PA-EC_{90}) against a reference HIV-1 isolate in cell culture. This target exposure concentration is based on the 5th percentile of C_{min} values in HIV-1 treatment trials in which CAB LA every 4 or 8 weeks in combination with RPV LA was shown to be effective in maintaining HIV-1 suppression in infected adults.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	viral analytes targeted by some diagnostic assays and an increase in the time required for individuals to develop anti-HIV-1 antibodies. While this phenomenon has been reported for other HIV-1 PrEP products, the potency and long-acting properties of CAB LA appear to amplify this issue. Across HPTN 083 and HPTN 084, 60% (12/20) of HIV-1 infections in the CAB arms compared 23% (18/77) of HIV-1 infections in the TDF/FTC arms had a delay of 1 or more visits before the local site detected HIV-1 infection relative to the retrospective testing by the central laboratory. The median (IQR) number of visits before the local site detected infection among the delayed cases was 4 (IQR: 2.25 to 5) in the CAB arm and 1 (IQR: 1 to 2) in the TDF/FTC arm. • The delay in HIV-1 diagnosis among individuals using CAB LA for PrEP means that there is a potential for HIV-infected individuals to have prolonged exposure to CAB monotherapy. This places individuals at risk for the development of INSTI resistance associated mutations (RASs). Further, individuals whose HIV-1 infection goes undiagnosed may be at increased risk of transmitting HIV-1, and perhaps INSTI-resistant variants, to sexual partners. Across trials HPTN 083 and HPTN 084, viruses harboring at least one major INSTI RAS were detected among 5/17 CAB participants with genotype data available. All 5 of these participants had experienced a delay in the time to diagnosis of HIV-1 infection. <u>Optional Oral Lead-In</u> • All participants in HPTN 083 and HPTN 084 received a 4-week CAB oral lead-in (OLI) prior to initiating long-acting CAB injections. The OLI was included in the trials as a conservative measure to assess drug tolerability and safety. No concerning safety events occurred during the OLI that would warrant requiring an OLI for all patients. As described above there were two pharmacologic failures in HPTN -083 that occurred during the OLI, highlighting the potential	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	detriment of the OLI in patients who have poor medication adherence. • Though a direct to injection (DTI) approach has not yet been studied in an HIV-1 PrEP setting, in the extension phase of the HIV-1 treatment trial, FLAIR, participants were given the choice to start with an OLI or move directly to CAB LA plus rilpivirine LA injections. Safety and efficacy were comparable among FLAIR participants who opted for an OLI and for those who opted for a DTI approach. Further, results of simulations indicated that that the contribution of the OLI to the plasma CAB concentrations is limited to the first week, suggesting that an OLI is not needed to achieve target plasma CAB concentrations.	

2.2. Conclusions Regarding Benefit-Risk

HIV-1 infection remains a major public health concern in the United States and abroad. While there are now many drugs available to treat HIV-1 infection safely and effectively, there is no cure. Preventing HIV-1 infection through PrEP is a key component of efforts to end the HIV epidemic. Currently approved options for HIV-1 PrEP all require once daily oral administration, and their effectiveness is closely tied to medication adherence. There is an interest among patients and the medical community to provide additional options for HIV-1 PrEP, with particular interest in options that are not as dependent on daily medication adherence. CAB long-acting (LA) is an injectable INSTI that is administered every 4 weeks (Q4W) for the first two doses and Q8W thereafter.

Across two large, randomized, double-blind, active-controlled trials, CAB LA was found to be superior to the currently approved HIV-1 PrEP regimen, TDF/FTC. Superior efficacy was demonstrated in men who have sex with men (MSM), transgender women, and cisgender women. Although the overall rate of HIV-1 seroconversions among participants receiving CAB was very low in both trials, six participants in HPTN 083 experienced HIV-1 seroconversion despite having what was thought to be adequate plasma CAB exposures and/or on-time CAB LA injections (referred to as pharmacologic failures). Also, of note, a greater proportion of HIV-1 seroconversions among CAB participants compared to TDF/FTC participants were associated with a delay in HIV-1 diagnosis. In five of the CAB participants with delayed HIV-1 diagnosis, the resultant prolonged exposure to CAB monotherapy led to the development of INSTI resistance-associated substitutions (RAS). The risk of pharmacologic failure, delayed HIV-1 diagnosis, and INSTI resistance will all be mitigated through frequent HIV-1 testing using more sensitive assays (to be described in labeling) as well as through a 5-year postmarket observational study that will be conducted as a postmarket requirement.

The safety evaluation of CAB LA was adequate, and the demonstrated safety profile of CAB LA is acceptable for the indicated dose and population. The overall safety profile of CAB LA is generally similar to other INSTIs, with the addition of frequent grade 1 and 2 ISRs. All participants in HPTN 083 and HPTN 084 received an OLI prior to initiating CAB LA injections. OLI dosing was safe, and few patients discontinued prior to the injection phase. The HPTN 083 and HPTN 084 extension trials (in which participants originally randomized to the TDF/FTC arm will be given the opportunity to switch to CAB LA with or without use of an OLI) as well as from the planned postmarket observational study will provide additional data regarding the direct to injection approach when CAB LA is used for HIV-1 PrEP.

Based on the totality of the data, the benefits of injectable CAB LA formulation for HIV-1 PrEP clearly outweigh the risks. The approval of CAB LA for HIV-1 PrEP will provide patients with a new option for HIV-1 prevention. Unlike currently approved PrEP regimens, CAB LA is not dependent on daily medication adherence. It is hoped that this novel approach to PrEP delivery will result in an increase in PrEP uptake and that this uptake will extend to patients/populations that have previously been reluctant to utilize PrEP due to the daily pill burden.

II. Interdisciplinary Assessment

3. Introduction

APRETUDE (cabotegravir (CAB)) extended-release injectable suspension is intended for use as HIV-1 pre-exposure prophylaxis (PrEP) in at-risk adults and adolescents weighing at least 35 kg. CAB, an integrase strand transfer inhibitor (INSTI), is not a new molecular entity. VOCABRIA (CAB tablets) and CABENUVA (CAB extended release injectable suspension copackaged with rilpivirine (RPV) extended-release injectable suspension) were approved for the treatment of HIV-1 infection on January 21, 2021.

Two similar phase 3 clinical trials, HPTN 083 (GSK 201738) and HPTN 084 (GSK 201739) are being conducted by the HIV Prevention Trials Network under sponsorship of the Division of Acquired Immunodeficiency Syndrome (DAIDS), National Institute of Allergy and Infectious Diseases/ National Institutes of Health. HPTN 083 was conducted to assess the safety and to establish the noninferiority (NI) of CAB injections compared to oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) among HIV-uninfected cisgender men and transgender women who have sex with men (MSM and TGW). HPTN 084 was conducted to assess the safety and to establish the superiority of CAB injections compared to oral TDF/FTC among HIV-uninfected cisgender women.

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

No key review issues relevant to evaluation of benefit were identified.

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Risk of Prolonged Exposures to CAB Monotherapy in Subjects who Become HIV-1 Infected

3.1.2.2. Optional Oral Lead-In

3.2. Approach to the Review

Table 4 provides an overview of the clinical trials to support the benefit-risk assessment of long-acting CAB (CAB LA) for HIV-1 PrEP and includes data from two similarly-designed phase 3 clinical trials, HPTN 083 and HPTN 084. Dose selection and the initial assessment of safety and antiviral activity of CAB came from phase 2 clinical trials (LATTE and LATTE-2) conducted in support of the CAB+RPV for HIV-1 treatment program. The phase 2 trials (HPTN 077 and ÉCLAIR) provided additional supportive safety data for CAB use not confounded by concurrent

RPV among HIV-uninfected adults. Lastly, the available safety and pharmacokinetic (PK) data from MOCHA, HPTN 083-01, and HPTN 084-01, were used to assess the risk-benefit of CAB LA use in adolescents (please see Section 8.3 on pediatrics for additional information).

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Table 4. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for CAB LA

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
HPTN 083 (NCT02720094)	HIV-1 uninfected MSM and TGW	Control type: AC Randomization: R Blinding: DB Biomarkers: None Innovative design features: None	Step 1: Arm A: Daily oral CAB (30-mg tablets) and oral TDF/FTC placebo for up to five weeks (N=2,281) Arm B: Daily oral TDF/FTC (300 mg/200 mg fixed-dose combination tablets) and oral CAB placebo for up to five weeks (N=2,285) Step 2: Arm A: CAB LA (600 mg as a single IM injection twice Q4W and Q8W thereafter) and daily oral TDF/FTC placebo to Week 180 Arm B: Daily oral TDF/FTC (300/200 mg fixed-dose combination tablets) and IM placebo twice Q4W and Q8W thereafter to Week 180 Step 3: Both arms: Open-label daily oral TDF/FTC for 48 weeks	Primary: Incident HIV-1 infections in Steps 1 and 2 Secondary (one of several): Resistance mutations to study products among seroconverters	Planned: 5,000 Randomized: 4,570 2,283, CAB group 2,287, TDF/FTC group	43 sites, 7 countries

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
HPTN 084 (NCT03164564)	Sexually-active, HIV-1 uninfected cisgender women at risk for HIV-1	Control type: AC Randomization: R Blinding: DB Biomarkers: None Innovative design features: None	Step 1: Arm A: Daily oral CAB (30-mg tablets) and oral TDF/FTC placebo for up to five weeks (N=1,614) Arm B: Daily oral TDF/FTC (300 mg/200 mg fixed-dose combination tablets) and oral CAB placebo for up to five weeks (N=1,610) Step 2: Arm A: CAB LA (600 mg as a single IM injection twice Q4W and Q8W thereafter) and daily oral TDF/FTC placebo to Week 180 Arm B: Daily oral TDF/FTC (300/200 mg fixed-dose combination tablets) and IM placebo twice Q4W and Q8W thereafter to Week 180 Step 3: Both arms: Open-label daily oral TDF/FTC for 48 weeks	Primary: Incident HIV-1 infections in Steps 1 and 2 Secondary: Resistance mutations to study products among seroconverters	Planned: 3,128 Randomized: 3,224 1,614, CAB group 1,610, TDF/FTC group	20 centers; 7 countries

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
HPTN 077 (NCT02178800)	HIV-1 uninfected men and women	Control type: PC Randomization: R Blinding: DB Biomarkers: NA Innovative design features: NA	Drug: CAB LA for injection; PBO for injection Dosage: Cohort 1: CAB 800 mg IM every 12 weeks; PBO IM every 12 weeks; Cohort 2: CAB 600 mg IM weeks 5, 9, 17, 25, and 33; PBO IM weeks 5, 9, 17, 25, and 33 Number treated: Cohort 1: 82; 28 Cohort 2: 69; 21 Duration (quantity and units): Cohort 1: 3 doses; Cohort 2: 5 doses	Primary: Safety and tolerability Secondary: Safety, tolerability, and PK; HIV incidence	Planned: 194 Randomized: 200 151, CAB group 49, placebo group	8 sites across 4 countries
ÉCLAIR (NCT02076178)	HIV-1 uninfected men	Control type: PC Randomization: R Blinding: DB Biomarkers: NA Innovative design features: NA	Drug: CAB LA for injection; PBO injection Dosage: CAB LA 800 mg IM every 12 weeks; PBO IM every 12 weeks Number treated: 105; 21 Duration (quantity and units): 3 doses	Primary: Safety Secondary: Safety, tolerability, and PK	Planned: 120 Randomized: 127 106, CAB group 21, placebo group	10 centers in US

Source: Reviewer
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled"
Abbreviations: AC, active control; BID, twice daily; CAB LA, long-acting cabotegravir; DB, double-blind; FTC, emtricitabine; MSM, men who have sex with men; N, number of subjects; NA, not applicable; OL, open-label; OLI, oral lead-in; PC, placebo-controlled; PK, pharmacokinetics; PO, by mouth; QD, once a day; R, randomized; TDF, tenofovir disoproxil fumarate; TGW, transgender women; US, United States

4. Patient Experience Data

In HPTN 083, participants completed a Study Medication Satisfaction Questionnaire (SMSQ) at Weeks 6, 10, 19, 27, 35, 43, 51, 59, 67, 75, 83, 91, 99, 107, 115, 123, 131, 139, 147, and Step 3, Day 0 if the questionnaire was not administered within the last 24 weeks. The SMSQ is a 12-item self-reported scale that measures overall satisfaction with medication.

In HPTN 084, participants completed brief behavioral surveys at enrollment and every 6 months thereafter. In addition, a subset of participants participated in a qualitative substudy that involved three in-depth interviews and semistructured observation in the waiting room(s) of the study clinic (according to the Applicant's clinical study report the results of the interviews and waiting room observations will be provided in a separate report).

The Applicant did not seek labeling based on any of the collected patient experience data. Therefore, these data were not reviewed in detail but are summarized briefly in Section 16.3.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	16.3
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

The clinical pharmacology review focused on assessment of CAB PK data to support an optional oral lead-in (OLI) (Section 7.7.2), and evaluation of CAB PK similarity following administration of the recommended dosing regimen to adolescents versus adults (Section 8.3).

Table 6. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic activity	
Established pharmacologic class (EPC)	CAB is an HIV-1 integrase strand transfer inhibitor (INSTI)
Mechanism of action	CAB inhibits HIV-1 integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration.
Antiviral activity	CAB had antiviral activity against laboratory strains (subtype B, n=4) with mean EC_{50} values of 0.22 to 1.7nM and against HIV-1 Group M subtypes A to G with median EC_{50} values ranging from 0.05 to 0.36nM (median EC_{50} value for subtype B =0.05nM).
Active moieties	CAB
QT prolongation	In a thorough QT study, cabotegravir did not prolong the QTc interval.
General information	
Bioanalysis	In studies HPTN 083 and HPTN 084, validated LC-MS/MS methods were used to measure CAB in human plasma (calibration range 25-25,000 ng/mL).
Healthy subjects versus patients	CAB exposures were not found to be significantly affected by HIV-1 infection status.

Characteristic	Drug Information
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	**Table 7. Pharmacokinetic Parameters Following Once-Daily Oral Cabotegravir and Following Initiation and Every-2-Month Continuation Intramuscular In ections of Cabote ravir**

Dosing Phase	Dosage Regimen	Geometric Mean (5th, 95th Percentile)[a]		
		$AUC_{(0\text{-}tau)}$[b] (mcg•h/mL)	C_{max} (mcg/mL)	C_{tau} (mcg/mL)
Oral lead-in[c]	30 mg once daily	145 (93.5, 224)	8.0 (5.3, 11.9)	4.6 (2.8, 7.5)
Initial injection[d]	600 mg IM initial dose	1,591 (714; 3,245)	8.0 (5.3, 11.9)	1.5 (0.65, 2.9)
Every-2-month injection[e]	600 mg IM every 2 months	3,764 (2,431; 5,857)	4.0 (2.3, 6.8)	1.6 (0.8, 3.0)

[a] Pharmacokinetic parameter values were based on individual post-hoc estimates from cabotegravir population pharmacokinetic models for patients in phase 3 treatment studies of HIV-1 treatment.
[b] tau is dosing interval: 24 hours for oral administration, 1 month for the initial injection, and 2 months for every 2 months for intramuscular injections of extended-release injectable suspension.
[c] Oral lead-in pharmacokinetic parameter values represent steady state.
[d] Initial injection C_{max} values primarily reflect oral dosing because the initial injection was administered on the same day as the last oral dose; however, $AUC_{(0\text{-}tau)}$ and the C_{tau} values reflect the initial injection. When administered without oral lead-in to HIV-1-infected recipients (n=110), the observed cabotegravir geometric mean (5th, 95th percentile) C_{max} (1-week post-initial injection) was 1.89 mcg/mL (0.438, 5.69) and C_{tau} was 1.43 mcg/mL (0.403, 3.90).
[e] Pharmacokinetic parameter values represent steady state.
Abbreviation: IM, intramuscular

Maximally tolerated dose or exposure	The highest CAB exposures were observed in a QT study where CAB 150 mg orally resulted in a mean C_{max} of 22.5 mcg/mL and mean $AUC_{0\text{-}24h}$ of 386 mcg·h/mL.
Dose proportionality	At oral doses of 5-60 mg, CAB exposures increased proportionally or slightly less than proportionally (within 15%). Comparing CAB 30 mg and 150 mg orally, C_{max} and AUC increased <3-fold, which is much less than proportionate with dose. At CAB LA doses of 100 mg to 800 mg, CAB exposures increased proportionally with dose.
Accumulation	After oral CAB 30 mg daily dosing, AUC accumulation (day 1 vs day 10) ratio is 2.5-fold. When comparing the initial injection and every two-month injection at steady-state, CAB AUC accumulation ratio is 1.18.
Time to achieve steady-state	Daily oral CAB reaches steady-state by day seven. Upon administration of the recommended PrEP injection dosing regimen, steady-state is reached by four weeks in males and 12 weeks in females.
Bridge between to-be-marketed and clinical trial formulations	The commercial oral and CAB LA formulations were used in HPTN 083 and HPTN 084.

Characteristic	Drug Information
Absorption	
Bioavailability	The absolute BA of oral or IM CAB is unknown. Relative bioavailability of CAB oral relative to the IM formulation is 76%.
T_{max}	Oral: 2 hours LA: 7 days
Food effect (fed/fasted) geometric least square mean and 90% CI	CAB 30 mg orally with a high-fat meal (53% fat, 870 calories) vs. fasted $AUC_{0-\infty}$: 1.14 (1.02, 1.28) C_{max}: 1.14 (1.03, 1.27) T_{max}: Median of 3.0 hours in both groups
Distribution	
Apparent volume of distribution	5.3 L
Plasma protein binding	99.9% bound at a CAB concentration range of 1–20 mcg/mL
Blood-to-plasma ratio	0.5
CSF-to-plasma concentration ratio (median [range])	0.003 (0.002–0.004)
Drug as substrate of transporters	CAB is a substrate of BCRP and P-gp. CAB is not a substrate of OATP1B1, OATP1B3, or OCT1
Elimination	
Mass balance results	27% of an oral CAB dose was eliminated in urine (0% unchanged), and 59% of the dose was eliminated in feces (47% unchanged)
Apparent clearance	0.151 L/h for both CAB oral and LA
Half-life (mean)	Oral: 41 hours LA: 5.6-11.5 weeks
Metabolic pathway(s)	CAB is primarily metabolized by UGT1A1, with a minor contribution by UGT1A9
Primary excretion pathways	Metabolism
Drug interaction liability (drug as perpetrator)	
Inhibition/induction of metabolism	CAB is not a clinically relevant inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 or UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B4, 2B7, 2B15, and 2B17. CAB is not an inducer of CYP1A2, 2B6 or 3A4.
Inhibition/induction of transporter systems	CAB is not a clinically relevant inhibitor of P-gp, BCRP, BSEP, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE 2-K, MRP2, or MRP4. CAB is an in vitro inhibitor of renal OAT1 and OAT3. However, based on PBPK modeling, no clinically relevant interaction is expected.

Abbreviations: BA, bioavailability; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CAB, cabotegravir; CI, confidence interval; EC_{50}, half-maximal effective concentration; IM, intramuscular; LA, long-acting; LC/MS/MS, liquid chromatography technique coupled with tandem mass spectrometry; PBPK, physiologically-based pharmacokinetic; P-gp, P-glycoprotein

5.1. Nonclinical Assessment of Potential Effectiveness

5.1.1. Trials HPTN 083 and HPTN 084

Nonclinical studies, including those describing CAB's mechanism of action, antiviral activity, and resistance, were submitted and reviewed under NDAs 212887 and 212888. No new studies were submitted to this NDA. However, two publications reporting the results of studies evaluating the ability of CAB LA to prevent the infection of rhesus macaques challenged intrarectally (Andrews et al. 2014) or intravaginally (Andrews et al. 2015) with chimeric simian/human immunodeficiency virus, were referenced. The studies demonstrated that CAB LA exhibited prophylactic activity under the tested conditions.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

6.1.1. HPTN 083 and HPTN 084

Dose Selection

The stated dose selection rationale for prevention of HIV-1 in the HPTN 083 and HPTN 084 protocols was to maintain plasma CAB concentrations above the protein-adjusted 90% inhibitory concentration (PA-IC_{90}) of 0.166 mcg/mL. However, at other times the Applicant refers to target concentrations of 4x PA-IC_{90}, i.e., ~0.65 mcg/mL.

In previous trials, CAB dosing of 800 mg intramuscular (IM) every 12 weeks resulted in a low fraction (~30%) of males with C_{tau} >0.65 mcg/mL after the first injection. 600 mg IM on Weeks 5, 9, and then every 8 weeks (Q8W), resulted in a large fraction (≥79%) of both males and females with C_{tau} >0.65 mcg/mL after the first and second injections (Table 8). These results supported the dosing regimen of CAB evaluated in HPTN083 and HPTN084.

Table 8. Fraction of Subjects With CAB C_{tau} >0.65 mcg/mL After the First and Second Injection in Previous Trials

Trial	Population	Injection Dosing	C_{tau} Timepoint	Fraction of Subjects With C_{tau} >0.65 mcg/mL
201120	HIV-uninfected men	800 mg IM on Weeks 5, 17, and 29	First injection	36%
HPTN 077	HIV-uninfected men	800 mg IM on Weeks 5, 17, and 29	First injection	28%
HPTN 077	HIV-uninfected women	800 mg IM on Weeks 5, 17, and 29	First injection	76%
HPTN 077	HIV-uninfected men	600 mg IM on Weeks 5, 9, 17, 25, and 33	First injection	95%
HPTN 077	HIV-uninfected men	600 mg IM on Weeks 5, 9, 17, 25, and 33	Second injection	80%
HPTN 077	HIV-uninfected women	600 mg IM on Weeks 5, 9, 17, 25, and 33	First injection	79%
HPTN 077	HIV-uninfected women	600 mg IM on Weeks 5, 9, 17, 25, and 33	Second injection	95%

Source: NDA 215499, SN 0002, Clinical Pharmacology Summary, Section 2.2. Subjects in trials 201120 and HPTN 077 received four-week OLI dosing and a one week washout period before starting injections.
Abbreviations: CAB, cabotegravir; IM, intramuscular

The dosing regimen evaluated in HPTN 083 and HPTN 084 (CAB 30 mg orally once daily on Month 1month one then 600 mg IM injections on Months 2, and every 2 months thereafter) maintains plasma trough concentrations of ≥0.65 mcg/mL for 95% of subjects.

Exposure-Response

The role of plasma CAB exposure as a predictor for HIV-1 infection in HPTN 083 and HPTN 084 is discussed in Section 7.7.1.

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. HPTN 083

6.2.1.1. Design, HPTN 083

HPTN 083 was a phase 2b/3, double-blind, randomized, controlled NI trial in HIV-uninfected cisgender men and transgender women who have sex with men (MSM and TGW). Participants were randomized 1:1 to Arm A (CAB) or Arm B (TDF/FTC). In Step 1 (OLI) of the trial, participants in Arm A received oral CAB 30 mg daily and oral TDF/FTC placebo daily for up to 5 weeks and participants in Arm B received oral TDF/FTC (300 mg/200 mg) daily and oral CAB placebo daily for up to 5 weeks. In Step 2, participants in Arm A received CAB LA 600 mg IM at two time points 4 weeks apart and 8 weeks thereafter, and oral TDF/FTC placebo daily through Week 153. Participants in Arm B received oral TDF/FTC (300 mg/200 mg) daily and IM placebo at two time points 4 weeks apart and every 8 weeks thereafter though Week 153. In Step 3, both arms were offered open-label oral TDF/FTC daily for 48 weeks.

The primary efficacy endpoint for HPTN 083 was the number of documented incident HIV-1 infection in Steps 1 and 2. The HIV-1 incidence rate was calculated as the total number of

participants with confirmed incident HIV-1 infection during study follow-up of Steps 1 and 2 (including time off randomized study product) up through 3 years from enrollment, divided by the person-years (PY) accumulated in each arm. Participants determined to be HIV-1 infected prior to randomization were excluded from the primary analysis.

Please refer to Section 15 for a detailed description of the protocol overview and conduct.

6.2.1.2. Eligibility Criteria, HPTN 083

HIV-1 negative MSM and TGW 18 years or older at high risk for sexually acquiring HIV-1 infection were eligible to participate in HPTN 083. High risk for sexually acquiring HIV-1 was defined as self-report of at least one of the following:

- Any condomless receptive anal intercourse in the 6 months prior to enrollment (condomless anal intercourse within monogamous HIV seronegative concordant relationship does not meet this criterion)
- More than five partners in the 6 months prior to enrollment (regardless of condom use and HIV-1 serostatus, as reported by the enrollee)
- Any stimulant drug use in the 6 months prior to enrollment
- Rectal or urethral gonorrhea or chlamydia or incident syphilis in the 6 months prior to enrollment
- SexPro score of ≤16 (U.S. sites only).

6.2.1.3. Statistical Analysis Plan, HPTN 083

The primary efficacy endpoint was the number of documented incident HIV-1 infections in Steps 1 and 2. The HIV-1 incidence rate was calculated as the total number of participants with confirmed incident HIV-1 infections during study follow-up of Steps 1 and 2 (including time off randomized study product), divided by the PY accumulated in each arm. For infected subjects, the time to HIV-1 seroconversion was calculated as the number of days between enrollment and the midpoint between the last HIV-negative visit and first HIV-1 positive visit, as determined by the Endpoint Adjudication Committee. The primary efficacy analysis was conducted on the modified intent-to-treat (mITT) population. This population included all randomized participants who were HIV-1 seronegative at baseline. HIV-1 seronegative participants at the screening visit who either became seropositive at the baseline visit or were retrospectively found to be HIV-1 seropositive at the enrollment visit prior to randomization were excluded from the mITT population. The participants were analyzed based on the randomized treatment. The hazard ratio (HR) and the p-value were calculated based on the Cox Proportional Hazard model, stratified by the research centers. In addition, the p-value calculated from the log-rank test was provided.

Assuming CAB LA was 25% more effective than TDF/FTC (with an expected HIV-1 incidence rate of 2.0/100 PY), approximately 172 observed HIV-1 infections would provide 90% power to rule out a NI margin of HR =1.23, with type-1 error alpha =0.025. The null and alternative hypotheses were defined as HR (CAB LA versus TDF/FTC) =1.23 and HR (CAB LA versus TDF/FTC) <1.23, respectively. The NI margin was an M2 margin that preserved 50% of the M1 margin based on a meta-analysis of three randomized controlled trials of TDF/FTC versus placebo in the MSM population. The total sample size needed was approximately 5,000, 2,500 per arm. According to the statistical analysis plan (SAP), following the Data Safety Monitoring

Board (DSMB) review in November 2019, the sample size was increased from 4,500 to 5,000, as documented in the DSMB recommendations.

Three interim analyses were scheduled with analysis times corresponding to when approximately ¼, ½, and ¾ of the estimated maximum number of HIV infections were observed, using the O'Brien-Fleming stopping bounds to control alpha spending. According to the SAP, it was initially planned to monitor the trial early for early stopping based on the interim monitoring boundary for superiority, or early evidence that oral CAB/CAB LA was definitively less effective than oral TDF/FTC. In light of the disruption to the dispensing of study drug caused by COVID-19 beginning in March 2020, the interim monitoring guidance was changed to recommend early stopping based on the NI boundary, i.e., to recommend stopping based on crossing the O'Brien-Fleming boundary for NI. The trial was stopped at the 1st interim analysis on May 14, 2020, with 52 adjudicated endpoints (HIV infections). The O'Brien-Fleming NI boundary was crossed, and the DSMB recommended that the blinded conduct of the trial be terminated. The cutoff date for this study in this NDA submission was May 14, 2020.

For more details, please refer to Section 15.

6.2.1.4. Results of Analyses, HPTN 083

This section summarizes the participant disposition, baseline demographics, clinical characteristics, and primary and key secondary efficacy results to support the efficacy of CAB LA in reducing HIV-1 seroconversion in the study population.

Disposition

A total of 6,449 participants were screened. Among them, 1,879 participants were screening failures, and 4,570 participants were randomized and comprised the randomized population. Among randomized participants, four subjects, one subject in CAB LA arm and three subjects in TDF/FTC arm, were inappropriately enrolled. By excluding these four subjects from the randomized population, the intent-to-treat population included 4,566 subjects: 2,282 in the CAB LA arm and 2,284 in the TDF/FTC arm. There were five subjects, two in the CAB LA arm and three in the TDF/FTC arm, identified postrandomization as baseline infections. Excluding these five subjects from the intent-to-treat population, the mITT population included 4,561 subjects, 2,280 in the CAB LA arm and 2,281 in the TDF/FTC arm (see Table 9).

Table 9. Summary of Analysis Populations, Randomized Population, Trial HPTN 083

Population Names	CAB (N=2,283) n (%)	TDF/FTC (N=2,287) n (%)
Randomized	2,283 (100%)	2,287 (100%)
ITT	2,282 (99.96%)	2,284 (99.87%)
mITT	2,280 (99.87%)	2,281 (99.74%)
Safety	2,281 (99.91%)	2,285 (99.91%)
Injection Step 2 efficacy population	2,109 (92.38%)	2,069 (90.47%)

Source: Statistical reviewer, ADSL and SAS software were used.
Abbreviations: CAB, cabotegravir; ITT, intent-to-treat; mITT, modified ITT; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 10 presents a summary of patient disposition at the end of the blinded study. Because the trial was stopped at the first interim analysis, approximately 96% of subjects were still ongoing, and about 3-4% of subjects had already discontinued from the study. The reasons for discontinuation from the study were similar between two arms.

Table 10. Patient Disposition of Study Status, Randomized Population, Trial HPTN 083

Study Status[1]	CAB (N=2,283) n (%)	TDF/FTC (N=2,287) n (%)
Ongoing	2,210 (96.8)	2,203 (96.3)
Reason for discontinuation from study	73 (3.2)	84 (3.7)
Schedule exit visit/End of study[2]	7	7
Death	4	7
Inappropriate enrollment	1	3
Investigator decision	1	3
Participant refused further participation	54	54
Participant relocated; no follow-up planned	2	4

Source: Statistical reviewer, ADSL and SAS software were used.
[1] This table was generated based on the ADSL and were slightly different from the Table 1 in CSR based on the ADDS.
[2] This is the same as the study completed. The remainder categories were reasons for termination from the study.
Abbreviations: CAB, cabotegravir; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Baseline Demographics and Clinical Characteristics

The demographic characteristics between the two treatment arms were balanced (Table 11). The median age was 26 years, and 67% were less than 30 years of age. In the mITT population, 72% of participants were non-White, 12% were transgender women, 84% had body mass index (BMI) less than 30 kg/m^2, and 37% were enrolled from the United States. The SexPro score, a good indicator for the risk of HIV-1 infection, was collected only in North and South America (80% of subjects in the mITT). The majority (85%) of participants who had their scores collected had a SexPro score ≤16.

Table 11. Baseline Demographic and Clinical Characteristics, mITT Population, Trial HPTN 083

Characteristics	CAB	TDF/FTC	Total
mITT population			
n	2,280	2,281	4,561
Age (year)			
Mean (SD)	28.0 (8.17)	28.2 (8.15)	28.1 (8.16)
Median (Q1, Q3)	26.0 (22, 32)	26.0 (22, 32)	26.0 (22, 32)
(Min, max)	(18, 69)	(18, 69)	(18, 69)
Age category 1, n (%)			
18-24	929 (40.7%)	911 (39.9%)	1,840 (40.3%)
25-34	940 (41.2%)	929 (40.7%)	1,869 (41.0%)
35-44	284 (12.5%)	313 (13.7%)	597 (13.1%)
45-54	103 (4.5%)	109 (4.8%)	212 (4.6%)
55-60	19 (0.8%)	17 (0.7%)	36 (0.8%)
60+	5 (0.2%)	2 (0.1%)	7 (0.2%)
Age category 2, n (%)			
<30	1,570 (68.9%)	1,506 (66.0%)	3,076 (67.4%)
≥30	710 (31.1%)	775 (34.0%)	1,485 (32.6%)
Cohort, n (%)			
MSM	2,011 (88.2%)	1,976 (86.6%)	3,987 (87.4%)
TGW	266 (11.7%)	304 (13.3%)	570 (12.5%)
Prefer not to answer	3 (0.1%)	1 (0.0%)	4 (0.1%)

Characteristics	CAB	TDF/FTC	Total
Race, n (%)			
American Indian or Alaska Native	615 (27.0%)	597 (26.2%)	1,212 (26.6%)
Asian	417 (18.3%)	406 (17.8%)	823 (18.0%)
Black or African American	565 (24.8%)	566 (24.8%)	1,131 (24.8%)
Mixed race	49 (2.1%)	54 (2.4%)	103 (2.3%)
Native Hawaiian or other Pacific Islander	5 (0.2%)	2 (0.1%)	7 (0.2%)
White	616 (27.0%)	649 (28.5%)	1,265 (27.7%)
Unknown	13 (0.6%)	7 (0.3%)	20 (0.4%)
Ethnicity, n (%)			
Hispanic or Latino	1,041 (45.7%)	1,064 (46.6%)	2,105 (46.2%)
Not Hispanic or Latino	1,239 (54.3%)	1,216 (53.3%)	2,455 (53.8%)
Not reported	--	1 (0.0%)	1 (0.0%)
SexPro score			
n	1,827	1,830	3,657
≤16, n %	1,552 (84.9%)	1,565 (85.5%)	3,117 (85.2%)
>16, n (%)	275 (15.1%)	265 (14.5%)	540 (14.8%)
Number of sexual partner >3 (median) at baseline			
n	2,073	2,046	4,119
≤3, n %	1,215 (58.6%)	1,199 (58.6%)	2,414 (58.6%)
>3, n (%)	858 (41.4%)	847 (41.4%)	1,705 (41.4%)
Number of condomless receptive anal sex >1 (median) at baseline			
n	1,379	1,329	2,708
≤1, n %	760 (55.1%)	731 (55.0%)	1,491 (55.1%)
>1, n (%)	619 (44.9%)	598 (45.0%)	1,217 (44.9%)
BMI at baseline category, n (%)			
<30	1,901 (83.6%)	1,937 (85.1%)	3,838 (84.3%)
≥30	373 (16.4%)	340 (14.9%)	713 (15.7%)
Region, n (%)			
Africa	78 (3.4%)	74 (3.2%)	152 (3.3%)
Asia	375 (16.4%)	377 (16.5%)	752 (16.5%)
Latin America	978 (42.9%)	982 (43.1%)	1,960 (43.0%)
USA	849 (37.2%)	848 (37.2%)	1,697 (37.2%)
Country, n (%)			
ARG	168 (7.4%)	168 (7.4%)	336 (7.4%)
BRA	395 (17.3%)	401 (17.6%)	796 (17.5%)
PER	415 (18.2%)	413 (18.1%)	828 (18.2%)
THA	275 (12.1%)	278 (12.2%)	553 (12.1%)
USA	849 (37.2%)	848 (37.2%)	1,697 (37.2%)
VNM	100 (4.4%)	99 (4.3%)	199 (4.4%)
ZAF	78 (3.4%)	74 (3.2%)	152 (3.3%)

Source: Statistical reviewer, ADSL and SAS software were used.
Abbreviations: ARG, Argentina; BMI, body mass index; BRA, Brazil; CAB, cabotegravir; mITT, modified intention-to-treat; MSM, cisgender men who have sex with men; N, number of participants in treatment group; n, number of participants with given characteristic; PER, Peru; SD, standard deviation; SE, standard error; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; TGW, transgender women; THA, Thailand; USA, United States of America; VNM, Vietnam; ZAF, South Africa

Primary Efficacy Endpoint

The Applicant's primary efficacy results were confirmed by the statistical review team and the study demonstrated statistical superiority of CAB LA compared to TDF/FTC in reducing HIV-1 seroconversion in the study population (Table 12). The bias-adjusted HR estimate, corrected for

early stopping, was 0.34 with 95% confidence interval (CI) (0.18, 0.62) and the seroconversion rate reduction estimate was 66% with 95% CI (38%, 82%).

Table 12. HIV-1 Seroconversion Rates and Hazard Ratio, Steps 1 and 2, mITT Population, Trial HPTN 083

Parameter		CAB (N=2,280)	TDF/FTC (N=2,281)	Results
Number of HIV-1 infected events		13	39	
PY of follow-up		3,211	3,193	
HIV-1 infection rate per 100 PY (95% CI)[1]		**0.40 (0.22, 0.69)**	**1.22 (0.87, 1.67)**	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]				**0.328 (0.18, 0.61)**
Superiority test p-value				0.0005
Noninferiority test p-value (NI margin=1.23)				<0.0001
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]				**67 (39, 82)**
Bias-adjusted, corrected for early stopping[4]	Hazard ratio (CAB vs. TDF/FTC) (95% CI)			**0.34 (0.18, 0.62)**
	Superiority test p-value			0.0005
	Noninferiority test p-value			<0.0001
	Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			**66 (38, 82)**

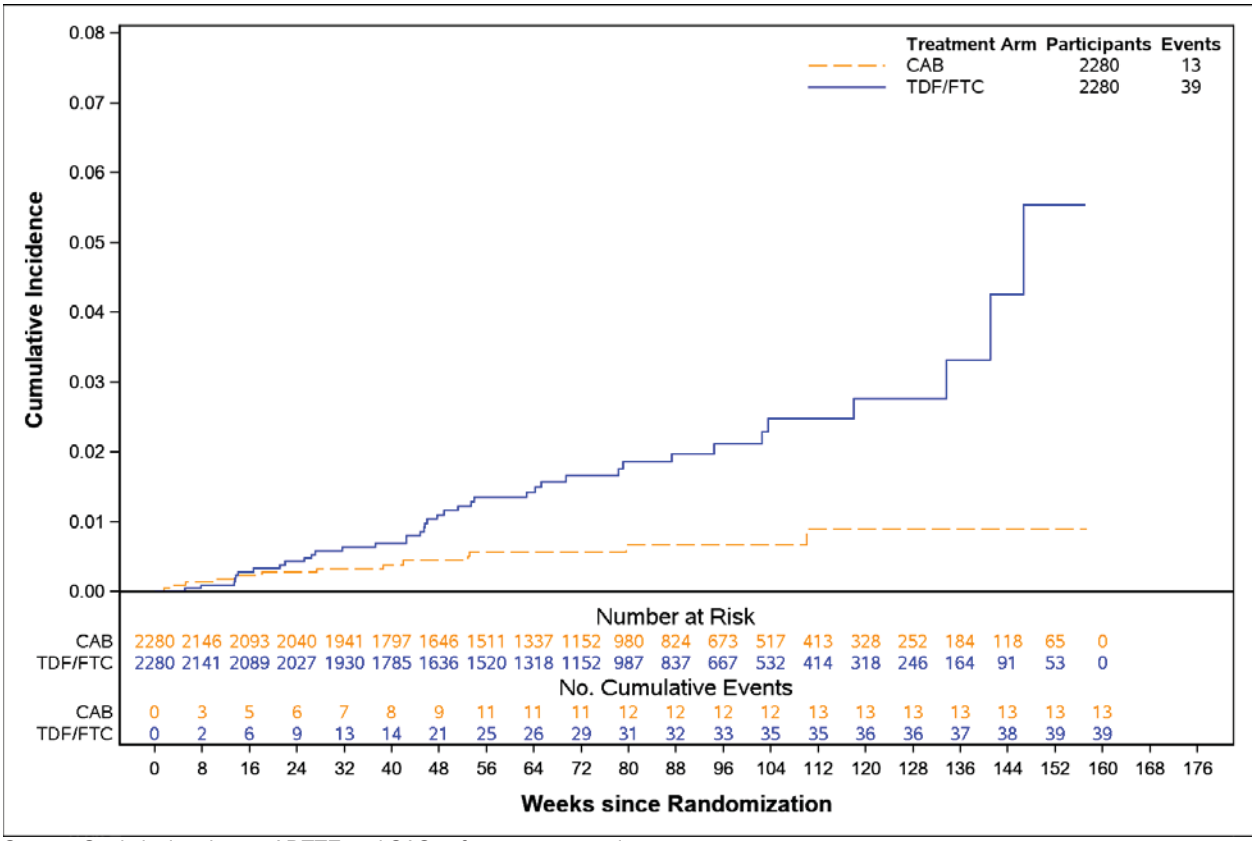
Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
[4] The bias-adjusted hazard ratio, CI and p-value account for the group-sequential trial design and the early stopping time.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; NI, noninferiority; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Sensitivity analyses were conducted in the injection Step 2 efficacy population and the on blinded study product population. The results were consistent with the primary analysis results. Please see Section 16.1.2 for details.

Secondary Efficacy Endpoint

The Kaplan-Meier curve for the cumulative incidence of HIV-1 seroconversion during Step 1 and 2 is shown in Figure 2. The cumulative incidence of HIV-1 seroconversion in the TDF/FTC arm was higher than that in the CAB LA arm after approximately 24 weeks of treatment.

Figure 1. Kaplan-Meier Curve of Time to HIV-1 Seroconversion, Step 1 and 2, mITT Population, Trial HPTN 083



Source: Statistical reviewer, ADTTE and SAS software were used.
Note: In the ADTTE data, one subject [redacted] (b) (6) (MSM, Black in USA) was randomized to TDF/FTC arm, but not treated, and had no follow-up time. The subject was ignored in the Cox model. As a result, TDF/FTC arm has 2,280 subjects in the Figure instead of 2,281 in the mITT.
Abbreviations: CAB, cabotegravir; mITT, modified intention-to-treat; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Subgroup Analyses of the Primary Efficacy Endpoint

Analyses were conducted to assess the treatment effect for subgroups defined by various demographic and clinical characteristics at baseline. For the primary efficacy endpoint, the HR estimates of seroconversion rates appeared consistent across most baseline subgroups of age, gender (MSM and TGW), race, region, and other baseline factors analyzed. See Section 16.1.3 for details.

Of note, the sample sizes for many subgroups were small, which limits the ability to detect trends with certainty. Numerous subgroup analyses were conducted without any adjustment for the multiple analyses, which could result in spurious findings due to chance.

6.2.2. HPTN 084

6.2.2.1. Design, HPTN 084

HPTN 084 was a phase 3, double-blind, randomized, safety and efficacy superiority trial of injectable CAB LA compared to daily oral TDF/FTC for pre-exposure prophylaxis in HIV-uninfected women. Participants were randomized 1:1 to Arm A (CAB) or Arm B (TDF/FTC) arm. The trial had three steps, which were the same as those in HPTN 083.

6.2.2.2. Eligibility Criteria, HPTN 084

HIV-1 negative individuals born female, 18-45 years of age, and at high risk for sexually acquiring HIV-1 infection were eligible to participate in HPTN 084. High risk for sexually acquiring HIV-1 was defined as a score of ≥5 on the modified Vaginal and Oral Interventions to Control the Epidemic (VOICE) scale (NOTE: Protocol version 1.0 (March 2, 2017) permitted enrollment of women who scored >2 using a modified VOICE risk score. Protocol version 1.0 was updated on November 6, 2019, to permit enrollment of women who scored ≥5 using a modified VOICE risk score to target women at higher risk of HIV-1 acquisition). Participants of childbearing potential were required to use a reliable form of long-acting contraception during the trial and for either 52 weeks after stopping the long-acting injectable or 30 days after stopping the oral study product.

6.2.2.3. Statistical Analysis Plan, HPTN 084

The primary efficacy endpoint was the number of documented incident HIV-1 infection in Steps 1 and 2. The HIV-1 incidence rate was calculated as the total number of participants with confirmed incident HIV-1 infection during study follow-up of Step 1and Step 2 (including time off randomized study product), divided by the PY accumulated in each arm. For infected subjects, the time to HIV-1 seroconversion was calculated as the number of days between enrollment and the midpoint between the last HIV-1-negative visit and first HIV-1-positive visit, as determined by the Endpoint Adjudication Committee. The primary efficacy analysis was conducted on the mITT population. This population included all randomized participants who were HIV-seronegative at baseline. HIV-seronegative participants at the screening visit who either became seropositive at the baseline visit or were retrospectively found to be HIV-seropositive at the enrollment visit prior to randomization were excluded from the mITT population. The participants were analyzed based on the randomized treatment. The HR and the p-value were calculated based on the Cox proportional hazards model, stratified by the research centers. In addition, the p-value calculated from the log-rank test was provided.

For the sample size calculation, the Applicant assumed that the background incidence rate in the absence of any PrEP was 3.5/100 PY. Both CAB LA and TDF/FTC were 85% effective with 100% adherence, and adherence rates for CAB LA and TDF/FTC were 80% and 48%, respectively, i.e., 1.12/100 PY for CAB LA and 2.07/100 PY for TDF/FTC. Given these assumptions, a total sample size of about 3,200, with approximately 114 observed HIV-infections with interim monitoring, would provide 90% power with type-1 error alpha =0.025. The null and alternative hypotheses were defined as HR (CAB LA versus TDF/FTC) =1.00 and HR (CAB LA versus TDF/FTC) ≠1.0, respectively.

The four interim analyses were planned with analysis times corresponding to when approximately 22%, 39%, 59%, and 78% of the estimated maximum number of HIV-1 infections had been observed, using the O'Brien-Fleming stopping bounds to control alpha spending. According to the submission, two interim analyses were conducted on November 5, 2019 and November 5, 2020, respectively. The trial was stopped at the second interim analysis that occurred on November 5, 2020, with 40 adjudicated endpoints (HIV-1 infections). The O'Brien-Fleming boundary had been crossed, and it was recommended by the DSMB that the blinded conduct of the trial be terminated. The cutoff date in this NDA submission is November 5, 2020.

For more details, please refer to Section 15.

6.2.2.4. Results of Analyses, HPTN 084

This section summarizes the participant disposition, baseline demographics, clinical characteristics, and primary and key secondary efficacy results to support the efficacy of CAB LA in reducing HIV-1 seroconversion in the study population.

Disposition

A total of 4,775 participants were screened. Among them, 1,551 participants were screening failures, and 3,224 participants were randomized and comprised the randomized population. Among randomized participants, 1,614 were randomized to the CAB LA arm and 1,610 were randomized to the TDF/FTC arm. The intent-to-treat (all randomized), mITT, and safety populations are identical (see Table 13).

Table 13. Summary of Analysis Populations, Randomized Population, Trial HPTN 084

Population Names	CAB (N=1,614), n (%)	TDF/FTC (N=1,610), n (%)
Randomized	1,614	1,610
ITT	1,614	1,610
mITT	1,614	1,610
Safety	1,614	1,610
Injection Step 2 efficacy population	1,495 (92.6%)	1,494 (92.8%)

Source: Statistical reviewer, ADSL and SAS software were used.
Abbreviations: CAB, cabotegravir; ITT, intent-to-treat; mITT, modified ITT; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 14 presents a summary of patient disposition at the end of the blinded study. As the trial was stopped as the 2nd interim analysis, 98% of subjects were still ongoing and less than 2% of subjects completed the study. The categories of completing/discontinued from study were similar between two arms.

Table 14. Patient Disposition of Study Status, ITT Population, Trial HPTN 084

Study Status[1]	CAB (N=1,614), n (%)	TDF/FTC (N=1,610), n (%)
Ongoing	1,587 (98.3)	1,586 (98.5)
Study completion	27 (1.7)	24 (1.5)
Categories of completing study		
Schedule exit visit/End of study[2]	1 (<1)	6 (<1)
Death	3 (<1)	0 (<1)
HIV-1 infection – Step 1[3]	1 (<1)	2 (<1)
Investigator decision	0	1 (<1)
Participant refused further participation	20 (1)	15 (<1)
Participant relocated; no follow-up planned	2 (<1)	0

Source: Statistical reviewer, ADSL and SAS software were used.
[1] This table was generated based on the ADSL and was slightly different from the Table 3 in CSR based on the ADDS.
[2] This is the same as the study completed. The rest of categories were reasons of subjects who terminated from the study.
[3] This was based on ADSL dataset. In ADTTE dataset, there were 4 infections at Step 1.
Abbreviations: CAB, cabotegravir; ITT, intent-to-treat; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Baseline Demographics and Clinical Characteristics

The demographic characteristics between the two treatment arms were balanced (Table 15). Almost all subjects (99%) were Black. The median age was 25 years, and 49% were less than 25 years of age. Most subjects (72%) had BMI less than 30 kg/m^2. Forty-one percent of participants were from South Africa (ZAF). The majority (80%) of participants had a screening modified VOICE risk score of ≥5, which is a good indicator of high-risk of HIV-1 infection in this population.

Table 15. Baseline Demographic and Clinical Characteristics, mITT Population, Trial HPTN 084

Characteristics	CAB	TDF/FTC	Total
mITT population			
n	1,614	1,610	3,224
Age (year)			
Mean (SD)	26.0 (5.7)	26.0 (5.8)	26.0 (5.8)
Median (Q1, Q3)	25.0 (22,29)	25.0 (22,30)	25.0 (22,30)
(Min, Max)	(18, 44)	(18, 45)	(18, 45)
Age category 1, n (%)			
18–25	929 (57.6%)	921 (57.2%)	1,850 (57.4%)
26–35	547 (33.9%)	554 (34.4%)	1,101 (34.2%)
36–45	138 (8.6%)	135 (8.4%)	273 (8.5%)
Age category 2, n (%)			
<25	800 (49.6%)	794 (49.3%)	1,594 (49.4%)
≥25	814 (50.4%)	816 (50.7%)	1,630 (50.6%)
Voice risk score at screening			
Mean (SD)	5.8 (1.6)	5.7 (1.5)	5.7 (1.6)
Median (Q1, Q3)	6 (5, 7)	6 (5, 7)	6 (5, 7)
(Min, Max)	(2, 8)	(2, 8)	(2, 8)
Voice risk score at screening group, n (%)			
<5	327 (20.3%)	345 (21.4%)	672 (20.8%)
≥5	1,287 (79.7%)	1,265 (78.6%)	2,552 (79.2%)
Race, n (%)			
Black or African	1,612 (99.9%)	1,606 (99.8%)	3,218 (99.8%)
White	--	1 (0.1%)	1 (0.0%)
Asian	2 (0.1%)	3 (0.2%)	5 (0.2%)
Self-identified gender, n (%)			
Female	1,612 (99.9%)	1,607 (99.8%)	3,219 (99.8%)
Male	--	3 (0.2%)	3 (0.1%)
Transgender male	2 (0.1%)	--	2 (0.1%)
Sex at birth, n (%)			
F	1,614 (100.0%)	1,610 (100.0%)	3,224 (100.0%)
Ethnicity, n (%)			
Not Hispanic/Latino	1,614 (100.0%)	1,610 (100.0%)	3,224 (100.0%)
BMI at baseline category, n (%)			
<30	1,149 (71.2%)	1,180 (73.3%)	2,329 (72.2%)
≥30	465 (28.8%)	430 (26.7%)	895 (27.8%)
Active syphilis infection			
n	1,611	1,608	3,219
Negative, n (%)	1,594 (98.9%)	1,584 (98.5%)	3,178 (98.7%)
Positive, n (%)	17 (1.1%)	24 (1.5%)	41 (1.3%)
Neisseria gonorrhea (urine)			
n	1,478	1,466	2,944
Negative, n (%)	1,375 (93.0%)	1,372 (93.6%)	2,747 (93.3%)
Positive, n (%)	103 (7.0%)	94 (6.4%)	197 (6.7%)
Neisseria gonorrhea			
n	1,601	1,587	3,188
Negative, n (%)	1,489 (93.0%)	1,488 (93.8%)	2,977 (93.4%)
Positive, n (%)	112 (7.0%)	99 (6.2%)	211 (6.6%)
Chlamydia trachomatis IgG antibody (urine)			
n	1,478	1,466	2,944
Negative, n (%)	1,183 (80.0%)	1,206 (82.3%)	2,389 (81.1%)
Positive, n (%)	295 (20.0%)	260 (17.7%)	555 (18.9%)

Characteristics	CAB	TDF/FTC	Total
Chlamydia trachomatis IgG antibody			
n	1,601	1,587	3,188
Negative, n (%)	1,277 (79.8%)	1,306 (82.3%)	2,583 (81.0%)
Positive, n (%)	324 (20.2%)	281 (17.7%)	605 (19.0%)
Trichomonas vaginalis			
n	1,577	1,553	3,130
Negative, n (%)	1,436 (91.1%)	1,424 (91.7%)	2,860 (91.4%)
Positive, n (%)	141 (8.9%)	129 (8.3%)	270 (8.6%)
Trichomonas vaginalis (rapid test)			
n	1,502	1,480	2,982
Negative, n (%)	1,361 (90.6%)	1,352 (91.4%)	2,713 (91.0%)
Positive, n (%)	141 (9.4%)	128 (8.6%)	269 (9.0%)
Hepatitis B surface antibody (HBsAB)			
n	1,608	1,605	3,213
Negative, n (%)	1,229 (76.4%)	1,161 (72.3%)	2,390 (74.4%)
Positive, n (%)	379 (23.6%)	444 (27.7%)	823 (25.6%)
Hepatitis B core antibody (HBcAB)			
n	1,612	1,608	3,220
Negative, n (%)	1,342 (83.3%)	1,316 (81.8%)	2,658 (82.5%)
Positive, n (%)	270 (16.7%)	292 (18.2%)	562 (17.5%)
Hepatitis B virus antibody (combined)			
n	1,608	1,603	3,211
HBSAB+_HBCAB+, n (%)	219 (13.6%)	246 (15.3%)	465 (14.5%)
HBSAB+_HBCAB−, n %	160 (10.0%)	196 (12.2%)	356 (11.1%)
HBSAB−_HBCAB+, n %	50 (3.1%)	45 (2.8%)	95 (3.0%)
HBSAB−_HBCAB−, n %	1,179 (73.3%)	1,116 (69.6%)	2,295 (71.5%)
Country, n (%)			
BWA	46 (2.9%)	45 (2.8%)	91 (2.8%)
KEN	31 (1.9%)	35 (2.2%)	66 (2.0%)
MWI	113 (7.0%)	111 (6.9%)	224 (6.9%)
SWZ	80 (5.0%)	80 (5.0%)	160 (5.0%)
UGA	300 (18.6%)	296 (18.4%)	596 (18.5%)
ZAF	653 (40.5%)	655 (40.7%)	1,308 (40.6%)
ZWE	391 (24.2%)	388 (24.1%)	779 (24.2%)

Source: Statistical reviewer, ADSL and SAS software were used.
Abbreviations: BMI, body mass index; BWA, Botswana; CAB, cabotegravir; IgG, immunoglobulin G; KEN, Kenya; mITT, modified intention-to-treat; MWI, Malawi; N, number of participants in treatment group; n, number of participants with given characteristic; SD, standard deviation; SE, standard error; SWZ, Swaziland; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; UGA, Uganda; ZAF, South Africa; ZWE, Zimbabwe

Primary Efficacy Endpoint

The Applicant's primary efficacy results were confirmed by the statistical review team, and the study demonstrated statistical superiority of CAB LA compared to TDF/FTC in reducing HIV-1 seroconversion in the study population (Table 16). The bias-adjusted HR estimate, corrected for early stopping, was 0.12 with 95% CI (0.05, 0.31) and the seroconversion rate reduction estimate was 88% with 95% CI (69%, 95%).

Table 16. HIV-1 Seroconversion Rates and Hazard Ratio for Step 1 and 2, mITT Population, Trial HPTN 084

Parameter		CAB (N=1,614)	TDF/FTC (N=1,610)	Results
Number of HIV-1 infected events		4	36	
PY of follow-up		1,961	1,946	
HIV-1 infection rate per 100 PY (95% CI)[1]		**0.20 (0.06, 0.52)**	**1.85 (1.30, 2.56)**	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]				**0.109 (0.04, 0.31)**
Superiority test p-value				<0.0001
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]				**89 (69, 96)**
Bias-adjusted, corrected for early stopping[4]	Hazard ratio (CAB vs. TDF/FTC) (95% CI)			**0.12 (0.05, 0.31)**
	Superiority test p-value			<0.0001
	Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			**88 (69, 95)**

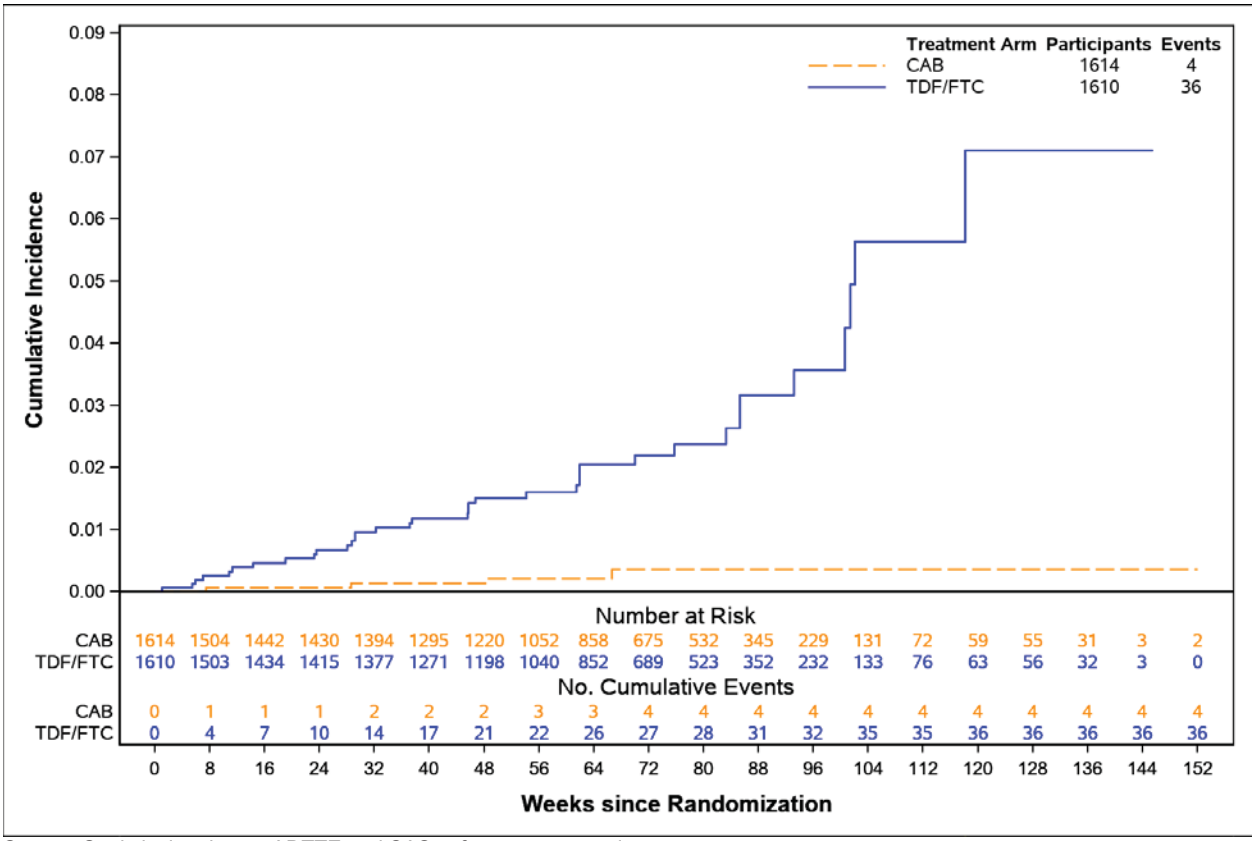
Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
[4] The bias-adjusted hazard ratio, CI and p-value account for the group-sequential trial design and the early stopping time.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Sensitivity analyses were conducted in the injection Step 2 efficacy population and the on blinded study product population. The results were consistent with the primary analysis results. Please see Section 16.1.2 for details.

Secondary Efficacy Endpoint

The Kaplan-Meier curve for the cumulative incidence of HIV-1 seroconversion during Steps 1 and 2 is shown in Figure 2. The cumulative incidence of HIV-1 seroconversion in the TDF/FTC arm was higher than that in the CAB LA arm after a few weeks of treatment.

Figure 2. Kaplan-Meier Curve of Time to HIV-1 Seroconversion, Steps 1 and 2, mITT Population, Trial HPTN 084



Source: Statistical reviewer, ADTTE and SAS software were used.
Abbreviations: CAB, cabotegravir; mITT, modified intention-to-treat; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Subgroup Analyses of the Primary Efficacy Endpoint

Analyses were conducted to assess the treatment effect for subgroups defined by various demographic and clinical characteristics at baseline. For the primary efficacy endpoint, the HR estimates of seroconversion rates appeared consistent across most baseline subgroups of age, BMI, baseline body weight, and other baseline factors analyzed. See Section 16.2.3 for details.

Of note, the sample sizes for many subgroups were small, which limits the ability to detect trends with certainty. Numerous subgroup analyses were conducted without any adjustment for the multiple analyses, which could result in spurious findings due to chance.

6.3. Key Review Issues Relevant to Evaluation of Benefit

Both HPTN 083 and HPTN 084 studies demonstrated that CAB LA is superior to TFD/FTC in preventing acquisition of HIV-1 infection in the studied populations. The review team concluded that the results of the phase 3 trials, HPTN083 and HPTN084 support the proposed indication in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection.

The review team did not identify any issues with assessing the benefit of CAB with respect to the primary efficacy endpoint (incident HIV-1 infections in Steps 1 and 2) in the studied populations.

The review issues relevant to the evaluation focus on development of resistance, pharmacologic failures, delayed seroconversion and optional use of an OLI. These review issues are discussed in Section 7.7.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

All pivotal nonclinical safety studies were submitted and reviewed under NDAs 212887 and 212888 for the treatment of HIV-1 infection. No additional nonclinical studies or data have been requested or are needed at this time. Overall, the nonclinical safety assessment for CAB was considered acceptable from a pharmacology/toxicology perspective to support approval for the present indication (HIV-1 PrEP).

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The potential safety concerns for CAB were identified based on the clinical experiences with other approved INSTI products and on the clinical experiences with CABENUVA and VOCABRIA. Notably, the applicability of CABENUVA safety concerns to CAB is confounded by the coadministration of RPV. Serious adverse reactions associated with INSTIs include hypersensitivity reactions (HSRs), hepatotoxicity, depressive disorders (including suicidal ideation, attempt, behavior, or completion), anxiety, and weight gain. Dolutegravir, a structurally similar INSTI to CAB may be associated with NTDs when used at the time of conception and early in pregnancy.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

None.

7.4. FDA Approach to the Safety Review

Predefined Safety Analysis Plans and Definitions for HPTN 083 and HPTN 084

The Applicant translated verbatim terms to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for the adverse events (AEs) reported in both trials. The translations were reviewed and generally found acceptable (several PTs were recoded).

The protocols specified use of the DAIDS toxicity scales for grading AEs. Version 1 of both the HPTN 083 protocol and HPTN 084 protocol stated that Version 2.0 (November 2014) of the

DAIDS Table for Grading Adult and Pediatric Adverse Events would be used for the duration of the study. However, in Version 2 of both HPTN 083 and HPTN 084 protocols, it was stated that Version 2.1 corrected (July 2017) of the DAIDS Table for Grading Adult and Pediatric Adverse Events would be used.

Efficacy and safety of the trials were monitored by a National Institute of Allergy and Infectious Diseases Data and Safety Monitoring Board. Additionally, an adjudication committee was established to assess liver-related AEs.

AEs were protocol-defined as: "An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product." Grade 1 and higher clinical AEs, Grade 2 and higher laboratory AEs, and any AE leading to a study product hold (temporary or permanent) were captured (of note, prior to HPTN 083 Letter of Amendment #4 dated December 14, 2017, only Grade 2 and higher clinical and laboratory AEs and AEs that led to study product hold were collected).

Adverse drug reactions (ADRs) were defined for the purpose of this review as any treatment-emergent AE (TEAE) considered by the investigator as related to the study drug within reasonable possibility.

AEs of special interest (AESIs) were determined for CAB based on preclinical and clinical experience, along with information from the INSTI drug class, and from CABENUVA and VOCARIA in particular.

Serious AEs (SAEs) were protocol-defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization (except for elective treatment of a pre-existing condition that did not worsen at baseline)
- Results in disability/incapacity
- Is a congenital anomaly/birth defect
- Other situations, including medical/scientific judgement or events that require invasive treatment (e.g., convulsions) that do not result in hospitalization

In addition to SAEs, expedited reporting was required in both HPTN 083 and HPTN 084 for the following AESIs:

- ALT (alanine transaminase) ≥3× upper limit of normal (ULN) AND total bilirubin ≥2×ULN
- Any seizure event

The safety data (AEs) were reported and entered into the database with the following prespecified phase designations:

- Step 1 on blinded study product (OBSP) covers the Blinded Oral Lead-In Phase and includes AE(s) with onset date between the date of randomization and the date of study drug discontinuation/study termination, date of first injection, date of unblinding, or 120

days postrandomization (whichever occurs first). Any AE that occurs while participant is on open-label TDF/FTC (OLT) is excluded from OBSP analysis.

- Step 2 OBSP (Injection Phase) covers the blinded injection phase and includes AE(s) with onset date on or after the first injection through 6 weeks (if only 1 injection is given) or 10 weeks (if 2 or more injections are given) after the last blinded injection OR before the first open-label pill dispensation during OLT Step 3, or before the start of antiretroviral therapy (ART) after seroconversion, or before the date of unblinding, whichever comes first. Any AE that occurs while participant is on OLT is excluded.
- Step 3 OLT will be referred to as the Tail Phase for safety analyses. Tail Phase includes the time from when a participant discontinues the blinded injection and continues for 48 weeks where participants are offered open-label TDF/FTC.
- Annual follow-up: No study drug or open-label product are administered. Annual follow-up visits for any participant who has discontinued treatment, has not seroconverted, has completed 48 weeks open-label TDF/FTC post last injection, if needed.

Data Used for Clinical Safety Assessment

The two phase 3 trials, HPTN 083 and HPTN 084, were the primary sources of safety data for this review. Data from these trials were analyzed individually to support the safety of CAB LA in HIV-negative MSM/TGW and cisgender women. Both phase 3 trials are ongoing and the cutoff date for the data in the primary safety analyses was May 14, 2020, and November 5, 2020, for HPTN 083 and HPTN 084, respectively. In addition, a 90-day safety update report (SUR) was submitted for HPTN 083 only (as agreed upon) on August 26, 2021. This SUR included a summary of new deaths, SAEs, AESIs, and AEs leading to study drug discontinuation occurring during the period from May 14, 2020, through March 31, 2021. AEs reported in the SUR are incorporated in the relevant safety sections of the review. The safety review for HPTN 083 and HPTN 084 will focus on the safety profile of the study products during the blinded study periods (i.e., Steps 1 and 2).

Phase 3 clinical trial data were independently analyzed by an OND clinical data scientist (CDS), and select analyses were conducted by the clinical reviewer in JMP v12 and JMP Clinical v6. The safety tables included in this section were created by the CDS or the clinical reviewer. All safety assessments and conclusions are those of the clinical review team unless otherwise specified.

Safety data from the phase 2 trials HPTN 077 and ÉCLAIR were also evaluated to support the safety of CAB LA. Please see Table 4 for a summary of the design of these trials. With the exception of Cohort 2 of HPTN 077, the CAB LA dosing regimens studied in the phase 2 trials (800 mg IM every 12 weeks) differed from that in the phase 3 trials (600 mg IM every 4 weeks (Q4W) x 2 doses, then Q8W). Therefore, these phase 2 safety data were not pooled with the phase 3 safety data. Review of data from these individual trials did not identify any additional safety concerns. Please see Section 17.6 for a summary of phase 2 safety data.

Reviewer's Approach to Safety Evaluation

Data from the two phase 3 trials were analyzed individually and were not pooled. This decision was based on a desire to provide population-specific safety profiles of CAB for MSM and

cisgender women patients in labeling. Within each trial, safety data were largely presented separately for each blinded study step (Step 1 and Step 2). This approach was chosen to allow for thorough characterization of the OLI to determine if any safety concerns were identified during the OLI that prevented participants from proceeding with CAB injections. These safety analyses by step were integral to our assessment of the acceptability of the Applicant's proposal to make the OLI optional. AEs occurring during nonblinded portions of the trials were not included in the main safety analyses.

The review team and the CDS did not identify any major data quality or integrity issues that precluded performing a safety review. No major issues were identified with respect to recording, coding, and categorizing AEs.

7.5. Adequacy of Clinical Safety Database

The CAB LA safety database is comparable to those used to support prior HIV-1 PrEP indications and is further supported by safety data from the CAB+RPV for HIV-1 treatment clinical trials. Therefore, the safety database is considered adequate for a comprehensive safety assessment of CAB LA for the proposed indication, patient populations, dosage regimen, and duration. Across HPTN 083 and HPTN 084, 3,895 participants were exposed to oral and/or injectable CAB. Of those, 3,636 participants were exposed to injectable CAB LA. An additional 256 participants were exposed to oral and/or injectable CAB in the phase 2 trials HPTN 077 and ÉCLAIR (though as noted previously different doses and frequencies of CAB LA were studied in these trials). Tables 17 and 18 summarize the exposure durations for the two phase 3 trials. Of note, the total exposure is presented in PY for HPTN 083 whereas it is reported in person-days in HPTN 084. The median exposure was comparable across arms in both trials. However, the total exposure on CAB was greater in HPTN 083 than HPTN 084 owing to the larger study population.

Table 17. Duration of Exposure, Safety Population, Trial HPTN 083

	CAB		TDF/FTC	
Parameter	Step 1 Tablet N=2,281	Step 2 Injection N=2,117	Step 1 Tablet N=2,285	Step 2 Tablet N=2,081
Duration of exposure, (weeks)				
Mean (SD)	4.1 (1)	72.1 (38.1)	4.6 (3.4)	73.5 (37.7)
Median (Q1, Q3)	4.1 (4, 4.3)	70.9 (41.3, 97.4)	4.1 (4.1, 4.3)	73 (41.7, 98.4)
Min, Max	0.1, 16.4	4.7, 156.1	0.1, 69.3	4.7, 161.6
Total exposure (person years)	179	2,926	201	2,933
Patients treated, by duration, n (%)				
<4 weeks	383 (16.8)	0	342 (15.0)	0
≥4 to <16 weeks	1,897 (83.2)	133 (6.3)	1,914 (83.8)	99 (4.8)
≥16 to <32 weeks	1 (0.04)	186 (8.8)	19 (0.8)	180 (8.6)
≥32 to <48 weeks	0	297 (14.0)	7 (0.3)	306 (14.7)
≥48 to <64 weeks	0	286 (13.5)	2 (0.09)	282 (13.6)
≥64 to <80 weeks	0	328 (15.5)	1 (0.04)	296 (14.2)
≥80 to <96 weeks	0	279 (13.2)	0	302 (14.5)
≥96 to <112 weeks	0	233 (11.0)	0	233 (11.2)
≥112 to <128 weeks	0	140 (6.6)	0	157 (7.5)
≥128 to <144 weeks	0	125 (5.9)	0	139 (6.7)
≥144 weeks	0	110 (5.2)	0	87 (4.2)

Source: adexsum.xpt; Software: R
Exposure duration shown is step 1 exposure only for step 1 groups and overall exposure for step 2 groups.
Abbreviations: CAB, cabotegravir; SD, standard deviation; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 18. Duration of Exposure, Safety Population, Trial HPTN 084

	CAB		TDF/FTC	
Parameter	Step 1 Tablet N=1,614	Step 2 Injection N=1,519	Step 1 Tablet N=1,610	Step 2 Tablet N=1,516
Duration of exposure, weeks				
Mean (SD)	70.2 (30)	72.9 (27.8)	70.7 (29.7)	72.8 (27.9)
Median (Q1, Q3)	70.6 (55.1, 89.1)	72.3 (56.3, 90)	71.3 (55.3, 89.4)	73 (56.4, 90)
Min, Max	0.3, 153.4	5, 153.4	0.3, 152.3	5, 152.3
Total exposure (person days)	793,506	775,125	796,928	772,443
Patients treated, by duration, n (%)				
<16 weeks	204 (12.6)	113 (7.4)	204 (12.7)	115 (7.6)
≥16 to <32 weeks	57 (3.5)	56 (3.7)	67 (4.2)	66 (4.4)
≥32 to <48 weeks	176 (10.9)	175 (11.5)	179 (11.1)	179 (11.8)
≥48 to <64 weeks	350 (21.7)	349 (23.0)	335 (20.8)	334 (22.0)
≥64 to <80 weeks	305 (18.9)	305 (20.1)	319 (19.8)	318 (21.0)
≥80 to <96 weeks	299 (18.5)	298 (19.6)	283 (17.6)	283 (18.7)
≥96 to <112 weeks	154 (9.5)	154 (10.1)	149 (9.3)	148 (9.8)
≥112 to <128 weeks	16 (1.0)	16 (1.1)	18 (1.1)	18 (1.2)
≥128 to <144 weeks	50 (3.1)	50 (3.3)	53 (3.3)	52 (3.4)
≥144 weeks	3 (0.2)	3 (0.2)	3 (0.2)	3 (0.2)

Source: adexsum.xpt; Software: R
Exposure duration shown is step 1 exposure only for step 1 groups and overall exposure for step 2 groups.
Abbreviations: CAB, cabotegravir; SD, standard deviation; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Safety Findings and Concerns, HPTN 083

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary, HPTN 083

A summary of the TEAEs in Steps 1 and 2 of HPTN 083 is presented in Table 19. The incidences of TEAES, severe AEs, and SAEs were similar in the CAB and TDF/FTC treatment groups in both Step 1 and Step 2. As previously noted, the OLI (Step 1) was included in the trial to allow for the identification of concerning safety events prior to the initiation of injectable (i.e., long-acting) CAB. There were no notable imbalances in safety events between the CAB and TDF/FTC arms during Step 1. There was a higher incidence of AEs leading to permanent treatment discontinuation in the CAB arm (5.2%) than in the TDF/FTC arm (3.6%) during Step 2 of HPTN 083. As discussed in detail in Section 7.6.1.4, this difference appears to have been driven by an increased rate of discontinuations due to local injection site reactions (ISRs) among participants in the CAB arm.

Table 19. Overview of Treatment-Emergent Adverse Events, Steps 1 and 2, Safety Population, Trial HPTN 083

Event	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Any TEAE[1]	1,508 (66.1)	2,072 (97.9)	1,564 (68.4)	2,009 (96.5)	1.3 (0.3, 2.3)
Severe	76 (3.3)	467 (22.1)	79 (3.5)	442 (21.2)	0.8 (-1.7, 3.3)
Moderate	1,076 (47.2)	1,316 (62.2)	1,087 (47.6)	1,291 (62.0)	0.1 (-2.8, 3.1)
Mild	329 (14.4)	69 (3.3)	359 (15.7)	40 (1.9)	1.3 (0.4, 2.3)
SAE	10 (0.4)	100 (4.7)	13 (0.6)	92 (4.4)	0.3 (-1.0, 1.6)
SAEs with fatal outcome	0	4 (0.2)	1 (0.04)	5 (0.2)	-0.1 (-0.3, 0.2)
Life-threatening SAEs	3 (0.1)	22 (1.0)	1 (0.04)	19 (0.9)	0.1 (-0.5, 0.7)
AE leading to permanent discontinuation of study drug	24 (1.1)	111 (5.2)	17 (0.7)	74 (3.6)	1.7 (0.4, 2.9)
AE leading to dose modification of study drug	16 (0.7)	93 (4.4)	22 (1.0)	116 (5.6)	-1.2 (-2.5, 0.1)
AE leading to interruption of study drug	16 (0.7)	93 (4.4)	22 (1.0)	115 (5.5)	-1.1 (-2.4, 0.2)
AE leading to reduction of study drug	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
AE leading to dose delay of study drug	0	0	0	0	0 (0, 0)

Source: adae.xpt; Software: R
[1] Includes treatment-emergent AE defined as any AE after the first dose of study drug and until 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively). For those with no injections, events after the first of 1 day after the date of discontinuation or 120 days after randomization were considered not treatment-emergent.
Duration is median 29 days for Step 1 groups and median 457 days for Step 2 groups.
Risk difference column shows difference (with 95% confidence interval) between step 2 groups.
Abbreviations: AE, adverse event; CAB, cabotegravir; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; TEAE, treatment-emergent adverse event

7.6.1.2. Deaths, HPTN 083

In HPTN 083, a total of four participants in the CAB arm had AEs that were fatal. All four of these fatal AEs occurred during Step 2. None of the four deaths among CAB participants were assessed by the investigators to be related to study drug. Following review of the submitted case narratives, the clinical review team agrees that none of these fatal AEs appear to have been drug-related. The fatal AEs are summarized briefly in Table 20. For a more detailed description of the fatal AEs reported among CAB participants, please see Section 17.1 in the Appendices.

Table 20. Fatal Adverse Events, Safety Population, Trial HPTN 083

Study Arm	Subject ID	Age	Sex	Study Day of Death	Cause of Death	
					Preferred Term	Verbatim Term
CAB Step 2	(b) (6)	18	M	368	Gunshot wound	Internal bleeding due to gunshot wound
CAB Step 2		32	M	426	Asphyxia	Mechanical asphyxia
CAB Step 2		22	M	226	Cardiopulmonary failure[1]	Cardiorespiratory failure
CAB Step 2		30	M	175	Traumatic hemorrhage	Homicide due to secondary traumatic bleeding
TDF/FTC Step 2		54	M	558	Cardiac disorder	Unspecified cardiac event
TDF/FTC Step 2		33	M	873	Multiple injuries	Multiple injuries
TDF/FTC Step 2		28	M	20	Stab wound	Left neck stab wound
TDF/FTC Step 2		33	M	74	Injury	Traumatic injuries
TDF/FTC Step 2		26	M	268	Cerebral hemorrhage	Cerebral bleed
TDF/FTC Step 2		45	M	182	Stab wound	Stab wound in one arm; cold arm

Source: adae.xpt; Software: R
[1] Cardiopulmonary failure thought to be due to a methamphetamine overdose (participant was found dead in his bathroom with a syringe and bag containing a clear crystal substance found at the scene).
Abbreviations: CAB, cabotegravir; F, female; ID, identification; M, male; NA, not applicable; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

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The SUR included seven new deaths (three in the CAB group and four in the TDF/FTC group). All narratives were reviewed, and the seven additional deaths are summarized in Table 21. Of interest, the narrative for the CAB participant experiencing a fatal myocardial infarction AE revealed that the participant was a 44-year-old man with a history of hypertension, binge drinking, and illicit drug use (including cocaine use), all of which were confounding factors for the myocardial infarction. No medical records or autopsy report were able to be obtained to provide additional information regarding the event. The clinical review team finds that based on the information available and the presence of known risk factors for myocardial infarction, this event was not clearly drug-related. The other two CAB deaths also did not appear to be drug-related. In conclusion, the fatal AEs reported in the SUR do not identify a new safety signal.

Table 21. Deaths Reported in the Safety Update Report, Trial HPTN 083

Participant ID	Treatment Group	List of adverse events (PT)	Time to onset (days)	Drug Related (as reported by the Investigator) yes /no	Drug Related (as assessed by GSK) (yes/no)	Additional Details (If Applicable)
(b) (6)	Cabotegravir	COVID-19	759	No	No	
	Cabotegravir	Multiple injuries	684	No	No	road traffic accident
	Cabotegravir	Myocardial infarction	1239	No	No	
	TDF/FTC	Unknown cause of Death	926	No	No	
	TDF/FTC	Asphyxia, Drowning	674	No	No	completed suicide.
	TDF/FTC	Cardiac arrest	871	No	No	
	TDF/FTC	Myocardial infarction	847	No	No	

Source: Applicant's Safety Update Report, Table 1.
Abbreviations: GSK, GlaxoSmithKline; PT, preferred term; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

7.6.1.3. Serious Adverse Events, HPTN 083

Overall, as shown previously in Table 19, the proportion of participants experiencing SAEs was similar in the CAB and TDF/FTC arms. There were no imbalances or apparent trends in SAEs reported in HPTN 083. For a complete listing of SAEs regardless of relatedness, please see Table 113. Drug-related SAEs were rare and were also balanced between groups (reported in 0.1% of participants in both the CAB and the TDF/FTC groups, Steps 1 and 2 events combined). Table 22 summarizes the drug-related SAEs for both treatment groups.

Table 22. Drug-Related Serious Adverse Events, Steps 1 and 2, Safety Population, Trial HPTN 083

Study Arm/ Step	Subject ID	Age	Preferred Term	Verbatim Term	Duration of Exposure (Days)	Fatal	Led to Treatment DC
CAB Step 1	(b) (6)	28	Suicide attempt	Suicide attempt	36	No	Yes
CAB Step 1		24	Suicide attempt	Unsuccessful suicide	27	No	Yes
			Affective disorder	Mood disorder	28	No	No
CAB Step 2		26	ITP	ITP	176	No	Yes
CAB Step 2		25	Seizure	Seizure	149	No	Yes
TDF/FTC Step 2		24	ALT increased	Elevated ALT	621	No	Yes
TDF/FTC Step 2		24	Suicide attempt	Multiple suicide attempts, substance use disorder	437	No	Yes
TDF/FTC Step 2		54	Cardiac disorder	Unspecified cardiac event	551	Yes[1]	NA

Source: ADAE dataset
[1] Participant experienced two cardiac disorder SAEs approximately 1 week apart. The first SAE was Grade 4 and the second SAE was Grade 5 (i.e., fatal). The action taken with study drug was reported as "not applicable" for both events, though participant was reported to be on study drug at the time of the events.
Abbreviations: Abbreviations: CAB, cabotegravir; DC, discontinuation; ID, identification; ITP, idiopathic thrombocytopenic purpura; M, male; NA, not applicable; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Additional details of interest regarding the drug-related SAEs reported among CAB participants are noted below:

- Drug-related suicide attempt SAEs were reported in two participants in the CAB group. Neither participant had reported a past medical history of depression or prior suicide attempt. Please see Section 7.6.3.4 for a more detailed review of psychiatric AEs.
- The idiopathic thrombocytopenia purpura SAE was confounded by concomitant ketorolac use, which is associated with inhibition of platelet function and thrombocytopenia. The thrombocytopenia persisted intermittently for more than a year after the participant stopped CAB.
- The seizure drug-related SAE occurred in a CAB participant with a history of a seizure approximately 10 years prior to study entry. Please see Section 7.6.3.5 for a detailed review of neurologic AEs.

The clinical review team concludes that it is possible the four SAEs in participants in the CAB group were drug-related. However, in the case of the seizure SAE, the history of a prior seizure is a significant confounding factor and in the idiopathic thrombocytopenia purpura case the concomitant ketorolac use is a confounding factor.

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The SUR included 96 new SAEs (46 in CAB group, 50 in TDF/FTC group) in 88 participants. No tabulation of these new SAEs was included in the SUR, but the Applicant notes that most of

the SAEs occurred in the Infections and infestations system organ class (SOC) (43%), Injury, poisoning and procedural complications SOC (12%), and Gastrointestinal disorders SOC (12%), and that "no obvious differences in the nature of SAEs between the CAB and TDF/FTC groups were noted." In addition, the SUR describes all serious AESIs that occurred during the reporting period and these events will be summarized below:

- Two participants in the CAB group and three participants in the TDF/FTC group had SAEs of suicide attempt during the SUR reporting period. One additional participant in the CAB group had an SAE of depression; no participants in the TDF/FTC group had an SAE of depression.
- One participant in the TDF/FTC group and no participants in the CAB group had an SAE of seizure during the reporting period.
- One participant in each group experienced an SAE of diabetic ketoacidosis during the reporting period, and one additional participant in the TDF/FTC group experienced an SAE of blood glucose increased. The CAB participant experiencing diabetic ketoacidosis had no history of diabetes but was noted to be obese and therefore at risk for diabetes.

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events, HPTN 083

Treatment discontinuations due to AEs, regardless of relatedness, are displayed in Table 23. Study drug discontinuations due to AEs were rare in both arms during Step 1 (1.1% and 0.7% in the CAB and TDF/FTC arms, respectively). The most commonly reported AE leading to treatment discontinuation during Step 1 was ALT elevation, which occurred at a similar rate in both arms. The majority of these ALT elevations were Grade 2 in severity, though there was one participant in each arm with a Grade 3 ALT elevation leading to treatment discontinuation (there were no Grade 4 ALT elevations leading to discontinuation. No ALT elevations leading to treatment discontinuation were assessed as serious and none were associated with Grade 2 or greater bilirubin elevation). Among subjects experiencing AEs leading to treatment discontinuation in Step 1, 12 CAB participants and 8 TDF/FTC participants discontinued treatment due to a drug-related AE. Drug-related AEs that led to treatment discontinuation in more than one CAB participant were dizziness and suicide attempt (in two participants each).

In Step 2 of HPTN 083, the incidence of AEs leading to treatment discontinuation was higher in the CAB group (5.2%) than in the TDF/FTC group (3.6%). This imbalance appears to have been driven largely by a higher rate of injection site pain AEs leading to discontinuation in the CAB group (2%) than in the TDF/FTC group (0%). The other AE that led to treatment discontinuation in >1% of participants was ALT increased. The incidence of ALT increased AEs leading to treatment discontinuation in Step 2 was balanced between groups. ISRs and liver-related events will be discussed in detail in Sections 7.6.3.1 and 7.6.3.3, respectively.

Table 23. Adverse Events Leading to Discontinuation in 2 or More Subjects, Safety Population, Trial HPTN 083

Event Category	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Patients with at least 1 AE leading to discontinuation	24 (1.1)	111 (5.2)	17 (0.7)	74 (3.6)	1.7 (0.4, 2.9)
Injection site pain	0	43 (2.0)	0	0	2.0 (1.4, 2.6)
Alanine aminotransferase increased	6 (0.3)	23 (1.1)	3 (0.1)	28 (1.3)	-0.3 (-0.9, 0.4)
Aspartate aminotransferase increased	2 (0.09)	5 (0.2)	0	8 (0.4)	-0.1 (-0.5, 0.2)
Creatinine renal clearance decreased	0	3 (0.1)	1 (0.04)	8 (0.4)	-0.2 (-0.6, 0.1)
Acute hepatitis C	1 (0.04)	5 (0.2)	0	3 (0.1)	0.1 (-0.2, 0.4)
Lipase increased	0	5 (0.2)	1 (0.04)	3 (0.1)	0.1 (-0.2, 0.4)
Acute hepatitis B	0	4 (0.2)	0	3 (0.1)	0.0 (-0.2, 0.3)
Seizure	0	2 (0.09)	2 (0.09)	3 (0.1)	-0.0 (-0.3, 0.2)
Hepatitis A	0	4 (0.2)	1 (0.04)	1 (0.05)	0.1 (-0.1, 0.3)
Blood creatine phosphokinase increased	1 (0.04)	1 (0.05)	0	2 (0.1)	-0.0 (-0.2, 0.1)
Injection site nodule	0	4 (0.2)	0	0	0.2 (0.0, 0.4)
Suicide attempt	2 (0.09)	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Amylase increased	0	1 (0.05)	0	2 (0.1)	-0.0 (-0.2, 0.1)
Fatigue	0	3 (0.1)	0	0	0.1 (-0.0, 0.3)
Injection site induration	0	3 (0.1)	0	0	0.1 (-0.0, 0.3)
Gastritis	0	0	1 (0.04)	1 (0.05)	-0.0 (-0.1, 0.0)
Injection site warmth	0	2 (0.09)	0	0	0.1 (-0.0, 0.2)
Malaise	0	2 (0.09)	0	0	0.1 (-0.0, 0.2)
Nausea	1 (0.04)	0	1 (0.04)	0	0 (0, 0)
Hepatic steatosis	0	0	0	2 (0.1)	-0.1 (-0.2, 0.0)
Hepatitis E	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Latent tuberculosis	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Blood creatinine increased	1 (0.04)	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Blood glucose increased	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Dizziness	2 (0.09)	0	0	0	0 (0, 0)
Depression	1 (0.04)	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Suicidal ideation	1 (0.04)	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Pruritus	0	1 (0.05)	1 (0.04)	0	0.0 (-0.0, 0.1)
Rash	1 (0.04)	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Rash pruritic	1 (0.04)	0	1 (0.04)	0	0 (0, 0)
Urticaria	0	0	2 (0.09)	0	0 (0, 0)

Source: [Clinical data scientist to provide all standard tables and figures]
[1] Coded as MedDRA preferred terms
Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event; PT, preferred term; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

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There were 50 AEs leading to study drug discontinuation in the SUR reporting period (29 in the CAB group, 21 in the TDF/FTC group). These occurred in 44 participants (25 in the CAB group and 19 in the TDF/FTC group). As was seen in the data presented in the main clinical study report, ALT elevation was a common reason for study drug discontinuation in the SUR. The frequency of ALT elevation AEs leading to treatment discontinuation was comparable across arms (10 and 11 participants in the CAB and TDF/FTC arms, respectively). Other AEs leading to treatment discontinuation in two or more participants were acute hepatitis C (n=7), amylase increased (n=2), aspartate aminotransferase increased (n=2) and lipase increased (n=2). Three CAB participants (compared to zero TDF/FTC participants) experienced an AE leading to treatment discontinuation that was assessed to be drug-related (Grade 3 electrocardiogram QT prolonged, Grade 2 nausea, and Grade 2 hypersensitivity). Of note, the hypersensitivity event involved the development of an urticarial rash 5 days after a participant's most recent CAB injection. The participant had a known history of urticaria to dipyrone and nonsteroidal anti-inflammatory medications, but he had not received these medications around the time of the AE.

7.6.1.5. Treatment-Emergent Adverse Events, HPTN 083

Please refer to Table 115 for a complete tabulation of TEAEs occurring in at least 1% of participants. In this section, TEAEs considered at least possibly related to study drug (i.e., adverse drug reactions, ADRs) are discussed. ADRs from Steps 1 and 2 for each arm are combined in Table 24, as this is how ADRs are presented in the label.

Table 24. Adverse Drug Reactions[1] by System Organ Class and Preferred Term, Terms Occurring in at Least 2% of Any Arm, Safety Population, Trial HPTN 083

System Organ Class Preferred Term	CAB N=2,281 n (%)	TDF/FTC N=2,285 n (%)	Risk Difference (95% CI)
Gastrointestinal disorders (SOC)	238 (10.4)	323 (14.1)	-3.7 (-5.6, -1.8)
Diarrhea	101 (4.4)	115 (5.0)	-0.6 (-1.8, 0.6)
Nausea	76 (3.3)	125 (5.5)	-2.1 (-3.3, -1.0)
General disorders and administration site conditions (SOC)	1,731 (75.9)	692 (30.3)	45.6 (43.0, 48.2)
Injection site pain	1,697 (74.4)	612 (26.8)	47.6 (45.1, 50.2)
Injection site nodule	263 (11.5)	13 (0.6)	11.0 (9.6, 12.3)
Injection site induration	255 (11.2)	6 (0.3)	10.9 (9.6, 12.2)
Injection site swelling	204 (8.9)	8 (0.4)	8.6 (7.4, 9.8)
Pyrexia	97 (4.3)	14 (0.6)	3.6 (2.8, 4.5)
Injection site erythema	63 (2.8)	11 (0.5)	2.3 (1.6, 3.0)
Injection site warmth	60 (2.6)	8 (0.4)	2.3 (1.6, 3.0)
Injection site bruising	63 (2.8)	25 (1.1)	1.7 (0.9, 2.5)
Fatigue	94 (4.1)	64 (2.8)	1.3 (0.3, 2.4)
Injection site pruritus	45 (2.0)	23 (1.0)	1.0 (0.3, 1.7)
Investigations (SOC)	771 (33.8)	831 (36.4)	-2.6 (-5.3, 0.2)
Lipase increased	51 (2.2)	51 (2.2)	0.0 (-0.9, 0.9)
Blood creatinine increased	166 (7.3)	169 (7.4)	-0.1 (-1.6, 1.4)
Creatinine renal clearance decreased	671 (29.4)	723 (31.6)	-2.2 (-4.9, 0.4)

System Organ Class Preferred Term	CAB N=2,281 n (%)	TDF/FTC N=2,285 n (%)	Risk Difference (95% CI)
Nervous system disorders (SOC)	133 (5.8)	175 (7.7)	-1.8 (-3.3, -0.4)
Headache	80 (3.5)	78 (3.4)	0.1 (-1.0, 1.2)
Sleep disorder	80 (3.5)	87 (3.8)	-0.3 (-1.4, 0.8)
Dizziness	45 (2.0)	64 (2.8)	-0.8 (-1.7, 0.1)
Psychiatric disorders (SOC)	109 (4.8)	111 (4.9)	-0.1 (-1.3, 1.2)
Sleep disorder	80 (3.5)	87 (3.8)	-0.3 (-1.4, 0.8)

Source: adae.xpt; Software: R
[1] Events shown are those assessed as treatment-related by the investigator.
Fatigue replaces: Malaise, Asthenia
Pyrexia replaces: Chills, Influenza like illness, Feeling hot
Sleep disorder replaces: Abnormal dreams, Insomnia, Nightmare, Initial insomnia, Poor quality sleep
Treatment-emergent adverse events defined as any AE after the first dose of study drug and until 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively). For those with no injections, events after the first of 1 day after the date of discontinuation or 120 days after randomization were considered not treatment-emergent.
Median duration is 457 days.
Risk difference column shows difference (with 95% confidence interval) between treatment and comparator.
Abbreviations: CAB, cabotegravir; CI, confidence interval; SOC, system organ class; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

As shown in Table 24, the most common ADRs were ISRs and these events were markedly more common among CAB participants than among TDF/FCT participants. These events will be discussed in detail in Section 7.6.3. With the exception of ISRs, most ADRs occurred in a similar proportion of CAB and TDF/FTC participants. Non-ISR ADRs that were at least 1% more common among participants in the CAB arm than in the TDF/FTC arm were pyrexia and fatigue. These are considered potential systemic injection reactions and will also be discussed in more detail in Section 7.6.3. Lastly, numerous preferred terms under the Investigations System Organ Class were reported as ADRs. (b) (4)

ADRs to be included in APRETUDE labeling are those that occurred in at least 1% of participants receiving CAB in either HPTN 083 or HPTN 084: ISRs, diarrhea, headache, pyrexia, fatigue, sleep disorders, nausea, dizziness, flatulence, abdominal pain, vomiting, myalgia, and rash.

7.6.1.6. Laboratory Findings, HPTN 083

The proportion of subjects with laboratory abnormalities representing a worsening from baseline in HPTN 083 are shown in Table 25, with additional laboratory parameters presented in Table 123 in the Appendices. The most commonly reported laboratory abnormality (any grade) was creatinine clearance decreased, which was reported among a higher proportion of TDF/FTC participants than among CAB participants. Creatinine increased abnormalities were numerically but not statistically more common among participants in the TDF/FTC arm than in the CAB arm. Notably, TDF/FTC carries a warning for new onset or worsening renal impairment. ALT and aspartate aminotransferase (AST) abnormalities were also common among participants in both arms. These transaminase abnormalities were typically Grade 1 or 2 in severity, and associated bilirubin and alkaline phosphatase abnormalities were uncommon.

Creatinine kinase and lipase elevations were reported frequently and occurred at a similar rate among subjects from both arms. See Section 7.6.3 for additional discussion regarding pancreatitis and rhabdomyolysis events.

Table 25. Key Laboratory Parameter Values Worsened From Baseline, Safety Population, Trial HPTN 083

Laboratory Parameter	CAB N=2,281 n (%)	TDF/FTC N=2,285 n (%)	Risk Difference (%) (95% CI)
Creatine kinase (IU/L) increased			
Any grade	769 (33.7)	774 (33.9)	-0.2 (-2.9, 2.6)
Grade 3-4	318 (13.9)	303 (13.3)	0.7 (-1.3, 2.7)
Lipase (IU/L) increased			
Any grade	401 (17.6)	434 (19)	-1.4 (-3.7, 0.8)
Grade 3-4	78 (3.4)	75 (3.3)	0.1 (-0.9, 1.2)
Creatinine clearance (mL/min) decreased			
Any grade	1,500 (65.8)	1,597 (69.9)	-4.1 (-6.8, -1.4)
Grade 3-4	156 (6.8)	187 (8.2)	-1.3 (-2.9, 0.2)
Creatinine (µmol/L) increased			
Any grade	428 (18.8)	473 (20.7)	-1.9 (-4.2, 0.4)
Grade 3-4	77 (3.4)	77 (3.4)	0 (-1, 1.1)
Alanine aminotransferase (IU/L) increased			
Any grade	585 (25.6)	674 (29.5)	-3.9 (-6.4, -1.3)
Grade 3-4	32 (1.4)	30 (1.3)	0.1 (-0.6, 0.8)
Aspartate aminotransferase (IU/L) increased			
Any grade	562 (24.6)	603 (26.4)	-1.8 (-4.3, 0.8)
Grade 3-4	58 (2.5)	68 (3)	-0.4 (-1.4, 0.5)
Bilirubin (µmol/L) increased			
Any grade	251 (11)	316 (13.8)	-2.8 (-4.7, -0.9)
Grade 3-4	8 (0.4)	15 (0.7)	-0.3 (-0.7, 0.1)
Alkaline phosphatase (IU/L) increased			
Any grade	41 (1.8)	82 (3.6)	-1.8 (-2.7, -0.9)
Grade 3-4	0	1 (0)	0 (-0.1, 0)
Triglycerides (mg/dL) increased			
Any grade	183 (8)	149 (6.5)	1.5 (0, 3)
Grade 3-4	14 (0.6)	8 (0.4)	0.3 (-0.1, 0.7)
Cholesterol (mg/dL) increased			
Any grade	170 (7.5)	91 (4)	3.5 (2.1, 4.8)
Grade 3-4	6 (0.3)	2 (0.1)	0.2 (-0.1, 0.4)
LDL cholesterol (mg/dL) increased			
Any grade	168 (7.4)	90 (3.9)	3.4 (2.1, 4.8)
Grade 3-4	22 (1)	8 (0.4)	0.6 (0.1, 1.1)

Source: ad b.xpt from submission 0010, received July 20, 2021; Software: R
Median duration is 457 days.
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CAB, cabotegravir; CI, confidence interval; LDL, low-density lipoprotein; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Abnormalities in several lipid parameters (triglycerides, total cholesterol, and low-density lipoprotein (LDL) cholesterol) were more common in CAB participants than in TDF/FTC participants. The majority of these abnormalities were Grades 1 and 2 in severity. To further explore the potential impact of CAB on lipid parameters, an analysis of the mean change from baseline in key lipid parameters was performed and is shown in Table 26. Changes from baseline to Month 15 and to Month 25 were analyzed. However, the proportion or participants with fasting lipid results available at Month 25 was low, therefore changes from baseline to Month 15 were the focus of the assessment. Among CAB participants, total cholesterol, LDL-cholesterol, and high-density lipoprotein (HDL)-cholesterol levels were stable from baseline to Month 15 and there was a very modest increase in triglycerides from baseline to Month 15. Conversely, among TDF/FTC participants, there was a modest improvement in total cholesterol and LDL-cholesterol

levels, a slight worsening of HDL-cholesterol levels, and no change in triglyceride levels from baseline to Month 15.

Table 26. Mean Change From Baseline in Fasting Lipid Analyte Values, Trial HPTN 083

	CAB			TDF/FTC		
Laboratory Parameter	Baseline mg/dL (# Participants With Data)	Month 15 Change (# Participants With Data)	Month 25 Change (# Participants With Data)	Baseline mg/dL (# Participants With Data)	Month 15 Change (# Participants With Data)	Month 25 Change (# Participants With Data)
Total cholesterol	169 (2245)	+1 (1341)	+4.5 (456)	167 (2234)	-11 (1338)	-7 (473)
LDL-cholesterol	101 (2242)	+1.3 (1338)	+3.7 (454)	99 (2233)	-6.4 (1337)	-3.6 (470)
HDL-cholesterol	50 (2245)	-0.85 (1341)	+0.1 (454)	49 (2234)	-3.5 (1338)	-3.5 (473)
Triglycerides	104 (2245)	+7.2 (1341)	+9.5 (456)	102 (2234)	+0.5 (1337)	+13 (473)

Source: ad b.xpt; Software: R
Abbreviations: CAB, cabotegravir; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Section 6 of the APRETUDE label will include Grade 3 and 4 laboratory abnormalities occurring in at least 1% of participants in either arm in either HPTN 083 or HPTN 084. Parameters that met this criterion for labeling are ALT, AST, creatine kinase (CK), lipase, and creatinine. In addition, given that even small differences in lipid parameters in the overall trial population could result in meaningful differences at the individual patient level, the review team recommends that lipid data (change from baseline) be included in the APRETUDE label, as was done for DESCOVY.

7.6.2. Safety Findings and Concerns, HPTN 084

7.6.2.1. Overall Treatment-Emergent Adverse Event Summary, HPTN 084

TEAEs from HPTN 084 in cisgender women are summarized in Table 27. Events are separated by study step. As shown, there are no notable imbalances between arms in Step 1 or Step 2.

Table 27. Overview of Treatment-Emergent Adverse Events, Steps 1 and 2, Safety Population, Trial HPTN 084

Event Category	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Any treatment-emergent AE[1]	1,285 (79.6)	1,479 (97.4)	1,289 (80.1)	1,461 (96.4)	1.0 (-0.2, 2.2)
Severe	35 (2.2)	205 (13.5)	49 (3.0)	203 (13.4)	0.1 (-2.3, 2.5)
Moderate	930 (57.6)	1,175 (77.4)	953 (59.2)	1,151 (75.9)	1.4 (-1.6, 4.4)
Mild	314 (19.5)	68 (4.5)	283 (17.6)	74 (4.9)	-0.4 (-1.9, 1.1)
SAE	1 (0.06)	24 (1.6)	8 (0.5)	25 (1.6)	-0.1 (-1.0, 0.8)
SAEs with fatal outcome	0	2 (0.1)	0	0	0.1 (-0.1, 0.3)
Life-threatening SAEs	0	4 (0.3)	2 (0.1)	11 (0.7)	-0.5 (-1.0, 0.0)
AE leading to permanent discontinuation of study drug	4 (0.2)	13 (0.9)	6 (0.4)	16 (1.1)	-0.2 (-0.9, 0.5)

Event Category	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
AE leading to dose modification of study drug	0	12 (0.8)	7 (0.4)	18 (1.2)	-0.4 (-1.1, 0.3)
AE leading to interruption of study drug	0	11 (0.7)	7 (0.4)	18 (1.2)	-0.5 (-1.2, 0.2)
AE leading to reduction of study drug	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
AE leading to dose delay of study drug	0	0	0	0	0 (0, 0)
Other	0	0	0	0	0 (0, 0)

Source: adae.xpt; Software: R
[1] Treatment-emergent adverse events defined as any AE with an onset date on or after the start of treatment and before 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively).
Duration is median 29 days for Step 1 groups and median 452 days for Step 2 groups.
Risk difference column shows difference (with 95% confidence interval) between step 2 groups.
Abbreviations: AE, adverse event; CAB, cabotegravir; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

7.6.2.2. Deaths, HPTN 084

There have been three fatal AEs reported in CAB participants in HPTN 084 to date and none reported in TDF/FTC participants. All deaths occurred in Step 2 and none were assessed to be drug-related. The deaths are summarized in Table 28 with additional key details provided in the text below the table.

Table 28. Fatal Adverse Events, Safety Population, Trial HPTN 084

Study Arm	Patient ID	Age	Sex	Study Day of Death	Cause of Death Preferred Term	Cause of Death Verbatim Term	Drug-Related
CAB Step 2	(b) (6)	21	F	199	Headache	Headache of unknown origin	No
CAB Step 2		30	F	301	Cerebrovascular accident	Cerebrovascular accident	No
CAB Step 2		33	F	102	Hypertensive heart disease	Hypertensive heart disease	No

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE with an onset date on or after the start of treatment and before 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively).
Duration is median 29 days for Step 1 groups and median 452 days for Step 2 groups.
Risk difference column shows difference (with 95% confidence interval) between step 2 groups.
For patient-level data, see the table "List of Adverse Events Leading to Death…"
Abbreviations: AE, adverse event; CAB, cabotegravir; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event

According to the Applicant's clinical study report, the headache and hypertensive heart disease fatal AEs were treatment-emergent, but the cerebrovascular accident was not treatment-emergent. However, the clinical review team did not agree with the Applicant's assessment. According to the clinical review team and the FDA CDS, the headache and cerebrovascular accident were treatment-emergent, fatal SAEs, but the hypertensive heart disease fatal SAE was not treatment-emergent. Please see the brief narratives below for additional details.

- Subject (b) (6): A previously healthy 21-year-old female developed a sudden, severe headache. She went to a clinic for evaluation and her initial work up was unrevealing. While awaiting additional evaluation, her family, who thought that the headache was due

to witchcraft, decided that she should be taken to her ancestral home. On her way there, she died. No autopsy was performed.

- Subject (b) (6) A 30-year-old female with a history of tobacco use presented after a syncopal episode with right hemiparesis and aphasia. She was diagnosed with a Grade 4 cerebrovascular accident (CVA). Her evaluation revealed a thrombus in the left common carotid artery with 100% internal carotid artery stenosis. She was also found to have polycythemia (unclear if this was a new or existing diagnosis). Study drug was withdrawn as a result of this AE. After 22 days, the Grade 4 CVA was considered resolved. She then experienced a fatal (Grade 5) CVA event on Day 301. Imaging at the time of this second CVA SAE showed a "large left middle cerebral infarct with hemorrhagic transformation and mass effect likely an extension of the initial insult." It appears that the Applicant is not considering this fatal CVA SAE to be treatment-emergent as it occurred after the study drug had been withdrawn following the nonfatal CVA SAE. However, as the fatal SAE appears to have been an extension of the treatment-emergent nonfatal SAE, this reviewer considers this death treatment-emergent.
- Subject (b) (6): A 33-year-old female with a history of hypertension missed multiple study visits and is believed to have stopped taking her antihypertensive medication. Then on Study Day 102 (b) (6)) she presented to a clinic with swollen legs, difficulty breathing, and high blood pressure. She died on the way from the clinic to the hospital. She had received her first and only CAB injection at her Week 5 study visit on (b) (6) She then missed her Week 9 study visit and injection. According to the Reviewer's Guide, given that she only received one injection, she is only considered to be on blinded study product for 6 weeks after the injection. Therefore, because the fatal AE occurred more than 6 weeks after her injection, the clinical review team concluded that the hypertensive heart disease event was not treatment-emergent.

This reviewer finds that there is insufficient information to assess causality for the fatal headache AE. The other fatal AEs, whether treatment-emergent or not, are confounded and do not appear treatment-related.

7.6.2.3. Serious Adverse Events, HPTN 084

The overall proportion of participants experiencing an SAE was similar across arms in both Steps 1 and Step 2; the rate of SAEs in Steps 1 and 2 combined was 1.5% and 2.0% in the CAB and TDF/FTC arms, respectively. No SOC or PT was disproportionally reported as SAEs to suggest a pattern. Hence, complete analysis of SAEs is not included in this section. Refer to Table 114 in the Appendices for this information. Treatment-related SAEs were rare in both arms; one CAB participant and three TDF/FTC participants experienced one or more treatment-related SAEs. The treatment-related SAE occurring in a CAB participant is summarized below.

- Subject (b) (6): A 23-year-old female participant experienced a Grade 3 respiratory tract infection AE on Study Day 546. Symptoms reported at the time of the event included cough, rhinorrhea, headache, joint aches, and vomiting. The event necessitated hospitalization and intravenous antibiotics. No action was taken with study drug and the event resolved. The provided rationale for the determination that the event was treatment-related was "no other cause could be attributed to the primary adverse event from the evaluations which were conducted."

A specific pathogen/cause is often not identified for respiratory tract infections. Given that the event occurred approximately 1.5 years after the initiation of study drug and that the event resolved despite ongoing study drug exposure, the clinical review team concludes that this event was not likely treatment-related.

7.6.2.4. Dropouts and/or Discontinuations Due to Adverse Events, HPTN 084

AEs leading to treatment discontinuation are summarized in Table 29. As shown, the only AEs leading to discontinuation in more than one participant were hepatitis A and ALT increased, both of which occurred at a similar rate across arms.

Table 29. Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial HPTN 083

System Organ Class Preferred Term	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Blood and lymphatic system disorders (SOC)	0	0	1 (0.06)	0	0 (0, 0)
Hypersplenism	0	0	1 (0.06)	0	0 (0, 0)
Hepatobiliary disorders (SOC)	0	1 (0.07)	0	1 (0.07)	-0.0 (-0.2, 0.2)
Hepatitis acute	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Hepatitis alcoholic	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Immune system disorders (SOC)	0	0	2 (0.1)	0	0 (0, 0)
Drug hypersensitivity	0	0	1 (0.06)	0	0 (0, 0)
Hypersensitivity	0	0	1 (0.06)	0	0 (0, 0)
Infections and infestations (SOC)	0	1 (0.07)	0	2 (0.1)	-0.1 (-0.3, 0.2)
Hepatitis A	0	1 (0.07)	0	2 (0.1)	-0.1 (-0.3, 0.2)
Investigations (SOC)	3 (0.2)	9 (0.6)	3 (0.2)	13 (0.9)	-0.3 (-0.9, 0.3)
Lipase increased	0	0	1 (0.06)	0	0 (0, 0)
Alanine aminotransferase increased	3 (0.2)	9 (0.6)	2 (0.1)	13 (0.9)	-0.3 (-0.9, 0.3)
Nervous system disorders (SOC)	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Cerebrovascular accident	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Psychiatric disorders (SOC)	1 (0.06)	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Suicidal ideation	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Sleep disorder	1 (0.06)	0	0	0	0 (0, 0)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE with an onset date on or after the start of treatment and before 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively).
Duration is median 29 days for Step 1 groups and median 452 days for Step 2 groups.
Risk difference column shows difference (with 95% confidence interval) between step 2 groups.
Abbreviations: CAB, cabotegravir; CI, confidence interval; SOC, system organ class; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

It is notable that there was a discrepancy in the number of participants reported to have discontinued study drug due to an AE in the disposition dataset (ADDS) and the AE dataset (ADAE). There were 15 more participants (7 CAB participants and 8 TDF/FTC participants) reported as having discontinued study drug due to AEs in the ADDS dataset than in the ADAE dataset. Based on communications with the Applicant (responses to IRs submitted to the NDA

on August 25, 2021, and September 8, 2021), it appears that participants who discontinued study drug due to a protocol-mandated clinical or laboratory discontinuation criterion or who discontinued study drug at the recommendation of the clinical management committee (CMC) were included as discontinuations due to an AE in the ADDS dataset but not in the ADAE dataset. The specific reasons for treatment discontinuation among these 15 discrepant participants were submitted and reviewed. Notably, in 4 of the 15 participants the exact reason for discontinuation could not be discerned from the available documentation. Though it seems many of these events that led to treatment discontinuation should have been reported as AEs in the ADAE dataset, the reporting of these events as AEs does not change the overall benefit-risk assessment for CAB LA.

7.6.2.5. Treatment-Emergent Adverse Events, HPTN 084

Please refer to Table 116 for a complete tabulation of common TEAEs, regardless of causality. No new safety concerns were identified in the analysis of all-causality TEAEs. In this section, TEAEs considered at least possibly related to study drug (i.e., ADRs) and occurring in at least 2% of participants in any arm are presented. ADRs from Steps 1 and 2 for each arm are combined in Table 30, as this is how ADRs are presented in the package insert. ADRs to be included in labeling are described in Section 7.6.1.5.

Table 30. Adverse Drug Reactions[1] by System Organ Class and Preferred Term, Terms Occurring in at Least 2% of Any Arm, Safety Population, Trial HPTN 084

System Organ Class Preferred Term	CAB N=1,614 n (%)	TDF/FTC N=1,610 n (%)	Risk Difference (95% CI)
Blood and lymphatic system disorders (SOC)	50 (3.1)	36 (2.2)	0.9 (-0.2, 2.0)
Neutropenia	32 (2.0)	17 (1.1)	0.9 (0.1, 1.8)
Gastrointestinal disorders (SOC)	202 (12.5)	283 (17.6)	-5.1 (-7.5, -2.6)
Abdominal pain	34 (2.1)	26 (1.6)	0.5 (-0.4, 1.4)
Diarrhea	63 (3.9)	71 (4.4)	-0.5 (-1.9, 0.9)
Vomiting	33 (2.0)	81 (5.0)	-3.0 (-4.3, -1.7)
Nausea	68 (4.2)	132 (8.2)	-4.0 (-5.6, -2.3)
General disorders and administration site conditions (SOC)	583 (36.1)	206 (12.8)	23.3 (20.5, 26.2)
Injection site pain	519 (32.2)	144 (8.9)	23.2 (20.5, 25.9)
Injection site swelling	105 (6.5)	5 (0.3)	6.2 (5.0, 7.4)
Injection site nodule	80 (5.0)	4 (0.2)	4.7 (3.6, 5.8)
Injection site induration	70 (4.3)	4 (0.2)	4.1 (3.1, 5.1)
Injection site pruritus	33 (2.0)	19 (1.2)	0.9 (-0.0, 1.7)
Fatigue	41 (2.5)	41 (2.5)	-0.0 (-1.1, 1.1)
Infections and infestations (SOC)	90 (5.6)	111 (6.9)	-1.3 (-3.0, 0.4)
Upper respiratory tract infection	62 (3.8)	72 (4.5)	-0.6 (-2.0, 0.7)

System Organ Class Preferred Term	CAB N=1,614 n (%)	TDF/FTC N=1,610 n (%)	Risk Difference (95% CI)
Investigations (SOC)	896 (55.5)	905 (56.2)	-0.7 (-4.1, 2.7)
Blood glucose increased	99 (6.1)	72 (4.5)	1.7 (0.1, 3.2)
Blood calcium increased	40 (2.5)	29 (1.8)	0.7 (-0.3, 1.7)
Blood creatinine increased	213 (13.2)	202 (12.5)	0.7 (-1.7, 3.0)
Aspartate aminotransferase increased	92 (5.7)	86 (5.3)	0.4 (-1.2, 1.9)
Blood glucose decreased	83 (5.1)	82 (5.1)	0.0 (-1.5, 1.6)
Alanine aminotransferase increased	114 (7.1)	119 (7.4)	-0.3 (-2.1, 1.5)
Blood calcium decreased	43 (2.7)	47 (2.9)	-0.3 (-1.4, 0.9)
Lipase increased	79 (4.9)	85 (5.3)	-0.4 (-1.9, 1.1)
Blood bilirubin increased	35 (2.2)	43 (2.7)	-0.5 (-1.6, 0.6)
Blood creatine phosphokinase increased	88 (5.5)	96 (6.0)	-0.5 (-2.1, 1.1)
Creatinine renal clearance decreased	692 (42.9)	699 (43.4)	-0.5 (-4.0, 2.9)
Amylase increased	252 (15.6)	264 (16.4)	-0.8 (-3.3, 1.7)
Blood alkaline phosphatase increased	25 (1.5)	38 (2.4)	-0.8 (-1.8, 0.1)
Blood phosphorus decreased	169 (10.5)	190 (11.8)	-1.3 (-3.5, 0.8)
Metabolism and nutrition disorders (SOC)	122 (7.6)	143 (8.9)	-1.3 (-3.2, 0.6)
Decreased appetite	37 (2.3)	58 (3.6)	-1.3 (-2.5, -0.1)
Nervous system disorders (SOC)	270 (16.7)	291 (18.1)	-1.3 (-4.0, 1.3)
Somnolence	35 (2.2)	26 (1.6)	0.6 (-0.4, 1.5)
Headache	190 (11.8)	213 (13.2)	-1.5 (-3.7, 0.8)
Dizziness	68 (4.2)	98 (6.1)	-1.9 (-3.4, -0.3)

Source: adae.xpt; Software: R
[1] Events shown are those assessed as treatment-related by the investigator.
Fatigue replaces: Malaise
Treatment-emergent adverse events defined as any AE after the first dose of study drug and until 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively).
Median duration is 452 days.
Risk difference column shows difference (with 95% confidence interval) between treatment and comparator.
Abbreviations: CAB, cabotegravir; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

As shown in Table 30, the most common treatment-related AEs were in the Investigations and General disorders and administration site conditions SOCs. Laboratory abnormalities are typically reported more objectively as laboratory findings rather than as AEs, and as such laboratory findings will be discussed in detail in Section 7.6.2.6. Most reported AEs under the General disorders and administration site conditions SOC are ISRs and will be discussed in detail in Section 7.6.3.1.

Among the remaining treatment-related AEs reported in HPTN 084, none of the events occurred at a ≥1% higher rate among CAB participants than TDF/FTC participants. However, it is notable that there was a statistically significant higher rate of treatment-related neutropenia events among CAB participants than among TDF/FTC participants, though rates were low overall (2.0% and 1.1% in the CAB and TDF/FTC arms, respectively; risk difference (95% CI) =0.9 (0.1, 1.8)). Please see Section 7.6.3.11 for further discussion regarding neutropenia AEs and neutrophil abnormalities across the CAB for HIV-1 PrEP trials.

7.6.2.6. Laboratory Findings, HPTN 084

The proportion of subjects with laboratory abnormalities representing a worsening from baseline in HPTN 084 are shown in Table 31 with additional laboratory parameters presented in Table 124 in the Appendices. As shown below, creatinine increased, ALT increased, and AST

increased abnormalities were common across both arms. However, there were no imbalances in any of these kidney or liver laboratory parameters across arms. Lipid abnormalities were uncommon overall and were exclusively Grade 1 and 2 abnormalities. In contrast to what was observed in HPTN 083, there were no imbalances in lipid parameters across arms. Grade 3 and 4 laboratory abnormalities occurring in at least 1% of participants in either arm in either HPTN 083 or HPTN 084 will be included in the APRETUDE label. Parameters that met this criterion for labeling are ALT, AST, CK, lipase, and creatinine.

Table 31. Key Laboratory Parameter Values Worsened From Baseline, Safety Population, Trial HPTN 084

Laboratory Parameter	CAB N=1,614 n (%)	TDF/FTC N=1,610 n (%)	Risk Difference (%) (95% CI)
Creatine kinase (IU/L) increased			
Any grade	231 (14.3)	255 (15.8)	-1.5 (-4, 0.9)
Grade 3-4	39 (2.4)	32 (2)	0.4 (-0.6, 1.4)
Lipase (IU/L) increased			
Any grade	191 (11.8)	164 (10.2)	1.6 (-0.5, 3.8)
Grade 3-4	7 (0.4)	7 (0.4)	0 (-0.5, 0.5)
Creatinine (µmol/L) increased			
Any grade	348 (21.6)	337 (20.9)	0.6 (-2.2, 3.5)
Grade 3-4	72 (4.5)	64 (4)	0.5 (-0.9, 1.9)
Alanine aminotransferase (IU/L) increased			
Any grade	217 (13.4)	225 (14)	-0.5 (-2.9, 1.8)
Grade 3-4	11 (0.7)	14 (0.9)	-0.2 (-0.8, 0.4)
Aspartate aminotransferase (IU/L) increased			
Any grade	207 (12.8)	176 (10.9)	1.9 (-0.3, 4.1)
Grade 3-4	15 (0.9)	12 (0.7)	0.2 (-0.4, 0.8)
Bilirubin (µmol/L) increased			
Any grade	63 (3.9)	65 (4)	-0.1 (-1.5, 1.2)
Grade 3-4	2 (0.1)	2 (0.1)	0 (-0.2, 0.2)
Alkaline phosphatase (IU/L) increased			
Any grade	36 (2.2)	53 (3.3)	-1.1 (-2.2, 0.1)
Grade 3-4	0	0	0 (0, 0)
LDL cholesterol (mg/dL) increased			
Any grade	39 (2.4)	34 (2.1)	0.3 (-0.7, 1.3)
Grade 3-4	0	0	0 (0, 0)
Cholesterol (mg/dL) increased			
Any grade	26 (1.6)	23 (1.4)	0.2 (-0.7, 1)
Grade 3-4	0	0	0 (0, 0)
Triglycerides (mg/dL) increased			
Any grade	25 (1.5)	19 (1.2)	0.4 (-0.4, 1.2)
Grade 3-4	0	0	0 (0, 0)

Source: ad b.xpt from submission 0012, received July 23, 2021; Software: R
Median duration is 452 days.
Based on DAIDS Adverse Event Grading Tables Version 2.1
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CAB, cabotegravir: CI, confidence interval; LDL, low-density lipoprotein; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Although there were no differences in lipid results across arms in HPTN 084, given that there were some differences by treatment arm in HPTN 083, an analysis of the mean change from baseline in key lipid parameters was performed to further explore the potential impact of CAB on lipid parameters in both trials. Changes from baseline to Month 15 and to Month 25 were analyzed. However, the proportion or participants with fasting lipid results available at Month 25

was low, so changes from baseline to Month 15 were the focus of the assessment. As presented below, between baseline and Month 15, participants in the CAB arm had stable total cholesterol, LDL-cholesterol, and HDL cholesterol, but experienced a modest increase in triglycerides. Comparatively, participants in the TDF/FTC arm had a modest decline in total cholesterol, LDL-cholesterol, and HDL-cholesterol, and had a small increase in triglycerides. For reasons outlined in Section 7.6.1.6, the review team recommends that changes in fasting lipid values from baseline to Month 15 be included in the APRETUDE label.

Table 32. Mean Change From Baseline in Fasting Lipid Analyte Values, Trial HPTN 084

	CAB			TDF/FTC		
Lipid Analyte	Baseline mg/dL (# Participants With Data)	Month 15 Change (# Participants With Data)	Month 25 Change (# Participants With Data)	Baseline mg/dL (# Participants With Data)	Month 15 Change (# Participants With Data)	Month 25 Change (# Participants With Data)
Total cholesterol	144 (1594)	+1 (907)	+5.2 (126)	146 (1582)	-4.8 (908)	+5.2 (123)
LDL-cholesterol	90 (1592)	-1.2 (907)	-1.7 (126)	92 (1580)	-5.6 (908)	-1.5 (123)
HDL-cholesterol	46 (1594)	-1.1 (907)	-1 (126)	47 (1581)	-2.2 (907)	-1 (123)
Triglycerides	64 (1594)	+5 (907)	+7.1 (126)	66 (1582)	+2.7 (908)	+6.6 (123)

Source: ad b.xpt; Software: R
Abbreviations: CAB, cabotegravir; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

7.6.3. Adverse Events of Special Interest, HPTN 083 and HPTN 084

The following AEs were recognized by the review team as potential safety-related review issues because signals were observed early in the development program for CABENUVA or the events are associated with use of other approved INSTI agents (e.g., bictegravir (BIC), dolutegravir (DTG), elvitegravir (EVG), or raltegravir (RAL)):

- Injection reactions
- HSRs and rash
- Hepatobiliary events
- Psychiatric events (including depressive disorders)
- Neurologic events (including seizure)
- Gastrointestinal events (including pancreatitis)
- Musculoskeletal events related to injection or rhabdomyolysis
- Weight gain
- Pregnancy and embryo-fetal toxicity

In addition, sexually transmitted infections (STIs) and neutropenia were assessed as potential safety issues.

None of these AESIs are considered to be key review issues warranting discussion in Section 7.7. Therefore, all AESIs will be covered in Section 7.6.3. Data for each AESI will be presented

separately for HPTN 083 and HPTN 084 (as well as for phase 2 trials where appropriate), with the conclusions and recommendations being drawn from the totality of data.

7.6.3.1. Injection Reactions

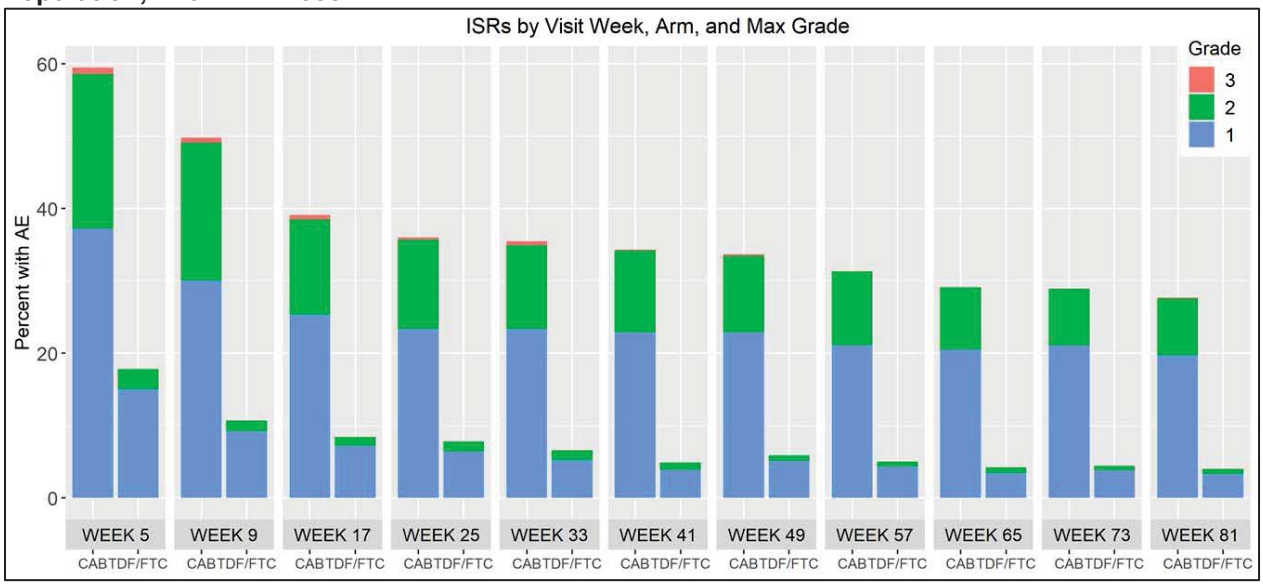
Local Injection Site Reactions

ISRs are a concern for all medications administered via an intramuscular injection. Not surprisingly, ISRs were common in both the CAB+RPV HIV-1 treatment clinical trials and in the CAB LA HIV-1 PrEP clinical trials. ISRs were markedly more common among HPTN 083 and HPTN 084 participants receiving injectable CAB LA compared to participants in the TDF/FTC arm who received an intralipid 20% fat emulsion placebo injection.

HPTN 083

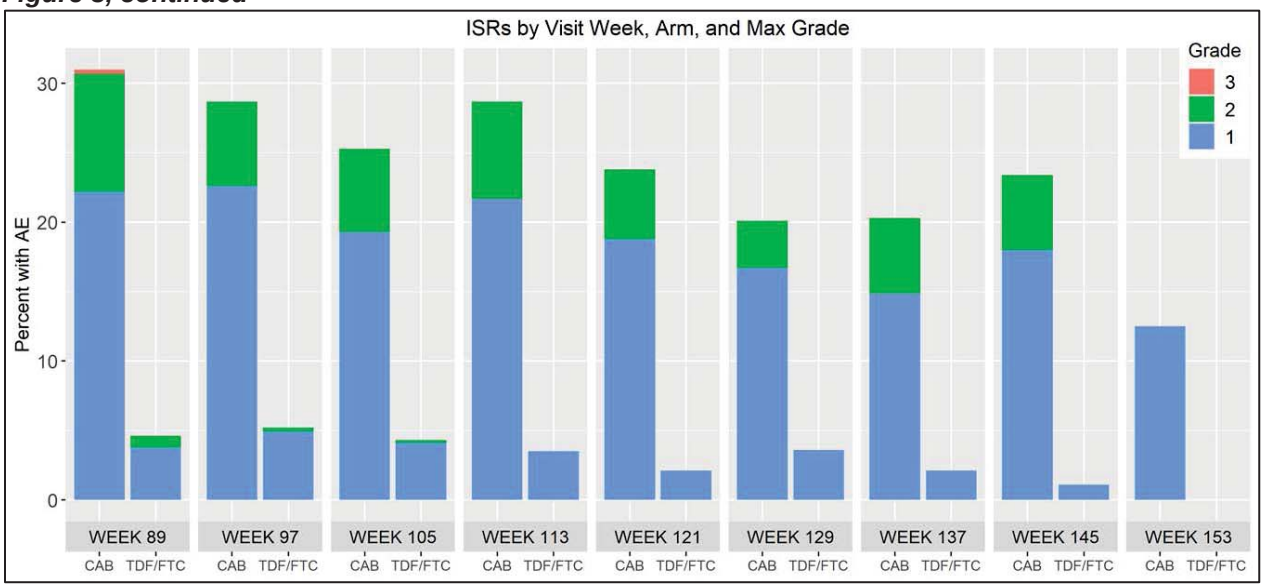
Overall, 82.2% of CAB participants and 34.8% of TDF/FTC participants experienced a local injection reaction. As shown in Figure 3, the frequency and severity of ISRs among CAB participants decreased over time. The most commonly reported ISRs (occurring in >10% of CAB participants) among CAB participants were injection site pain (80.9%), injection site nodule (12.4%), and injection site induration (12%) (see Table 119 for details). Injection site abscesses were rare, reported in only two CAB participants and no TDF/FTC participants. The majority of ISRs were Grade 1 or 2 in severity. Fifty-four (2.6%) CAB and 0 TDF/FTC participants experienced a Grade 3 ISR, and no participants experienced a Grade 4 ISR. There were no serious ISRs in either arm. Lastly, ISRs led to treatment discontinuation in 47 (2.2%) of CAB participants and 0 TDF/FTC participants.

Figure 3. Injection Site Reactions Over Time by Maximum Grade, Weeks 89 to 153, Injection Safety Population, Trial HPTN 083



Continued

Figure 3, continued

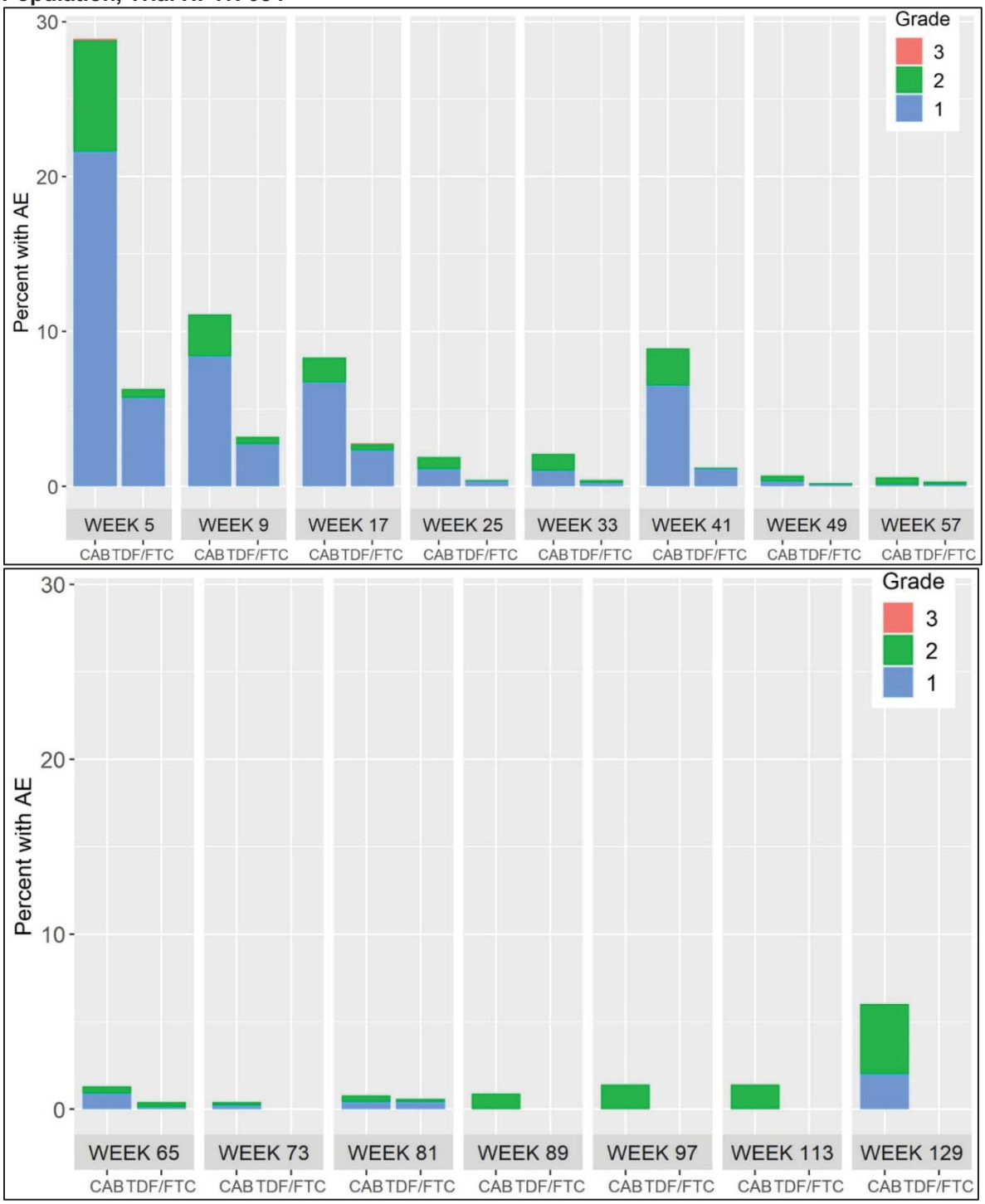


Source: adaeisr.xpt; Software: R
Percentages are based on subjects remaining in group at visit.
Abbreviations: AE, adverse event; CAB, cabotegravir; ISR, injection site reaction; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

HPTN 084

ISRs were reported among 38.1% and 10.9% of CAB and TDF/FTC participants respectively. As shown in Figure 4, the rate and severity of ISRs was greatest at Week 5 and then generally declined over the course of the trial. The most commonly reported ISRs (occurring in >5% of CAB participants) among CAB participants were injection site pain (34.2%), injection site swelling (6.8%), and injection site nodule (5.3%). Please see Table 120 for a detailed listing of reported ISRs in HPTN 084. Injection site abscesses were uncommon, occurring in 10 (0.7%) CAB participants and 5 (0.3%) TDF/FTC participants. Four of the CAB participants with an injection site abscess had a maximum AE grade of 2 and six participants had a maximum AE grade of 2. Overall, the majority of the ISRs were Grade 1 or 2 in severity. Only one participant in each arm experienced a Grade 3 ISR, and no participants experienced a Grade 4 ISR. No participant in either arm discontinued study treatment due to an ISR

Figure 4. Injection Site Reactions Over Time by Maximum Grade, Weeks 89 to 153, Injection Safety Population, Trial HPTN 084



Source: adaeisr.xpt; Software: R
Percentages are based on subjects remaining in group at visit.
Abbreviations: AE, adverse event; CAB, cabotegravir; ISR, injection site reaction; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Though cross-trial comparisons are generally discouraged, it is striking how much less frequent ISRs were among women in HPTN 084 compared to men and transgender women in HPTN 083.

Some potential explanations for this finding are differences in reporting of ISRs by gender and by region (HPTN 084 was conducted exclusively in Africa whereas HPTN 083 was conducted at sites in South America, North America, Africa, and Asia) as well as differences in subcutaneous fat thickness by gender and by region.

Systemic Injection Site Reactions

Pyrexia, musculoskeletal events, syncope/presyncope and sciatica were identified as potential systemic injection reactions in the CABENUVA clinical trials. Multiple exploratory analyses were conducted using data from HPTN 083 and HPTN 084 to identify potential additional AEs that could represent systemic ISRs.

HPTN 083

In an analysis of pyrexia, sciatica, syncope, and musculoskeletal AEs occurring in Step 2, we found that pyrexia events, but not musculoskeletal, syncope, or sciatica events, were more common among CAB participants than among TDF/FTC participants. It is important to note that this analysis did not take into account the timing of the events relative to the timing of injection.

Table 33. Potential Systemic Injection Reactions, Step 2, Safety Population, Trial HPTN 083

Reaction Type	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Musculoskeletal pain (GQ)	358 (16.9)	353 (17.0)	-0.1 (-2.3, 2.2)
Pyrexia (GQ)	275 (13.0)	136 (6.5)	6.5 (4.7, 8.2)
Sciatica (PT)	8 (0.4)	8 (0.4)	-0.0 (-0.4, 0.4)
Syncope (PT)	9 (0.4)	7 (0.3)	0.1 (-0.3, 0.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE after the first dose of study drug and until 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively). For those with no injections, events after the first of 1 day after the date of discontinuation or 120 days after randomization were considered not treatment-emergent.
Group query Musculoskeletal pain contains: Muscle strain, Pain in extremity, Back pain, Musculoskeletal chest pain, Myalgia, Musculoskeletal pain, Muscle spasms, Neck pain, Tendonitis, Rhabdomyolysis, Musculoskeletal stiffness, Patellofemoral pain syndrome, Tendon pain, Temporomandibular joint syndrome, Pain in jaw, Tendon disorder, Plantar fasciitis, Groin pain, Muscle tightness, Chondritis, Intervertebral disc disorder, Spinal stenosis, Osteoarthritis, Intervertebral disc protrusion, Joint swelling, Metatarsalgia, Tenosynovitis stenosans, Osteochondritis, Torticollis, Spinal pain, Rotator cuff syndrome, Bone pain, Bursitis, Musculoskeletal discomfort, Limb discomfort, Medial tibial stress syndrome, Costochondritis, Muscle discomfort, Intervertebral disc degeneration, Spinal osteoarthritis, Joint effusion, Periarthritis, Intervertebral disc displacement, Facet joint syndrome, Myositis, Enthesopathy.
Group query Pyrexia contains: Influenza like illness, Pyrexia, Chills, Feeling hot.
Abbreviations: CAB, cabotegravir; CI, confidence interval; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

To identify additional events that could represent systemic injection reactions, analyses of all AEs occurring within 1 day after an injection and within 7 days after an injection were conducted among participants in the injection safety population of HPTN 083. Specifically, AEs within 1 day of injection were defined as events with a start date on an injection date or the day after an injection date. AEs within 7 days of injection were defined as events with a start date equal to or greater than an injection date and less than or equal to the same injection date plus 7 days. AEs (excluding ISRs) that were more common among participants in the CAB arm than in the TDF/FTC arm are displayed in Tables 34 and 35. As shown pyrexia, malaise, fatigue, and chills AEs were more frequently reported within both 1 day and within 7 days after an injection among CAB participants compared to TDF/FTC participants. This temporal relationship suggests that in at least some cases these events represent a systemic reaction to an injection. Influenza like

illness, myalgia, headache, dermatitis, and hypertension were also more commonly reported within 7 days after an injection (but not within 1 day after an injection) in CAB participants than in TDF/FTC participants, suggesting that these events may also be causally related to the injection. The increased frequency of certain investigation AEs (e.g., low-density lipoprotein increased and blood cholesterol increased) are of uncertain significance and seem less likely to be a direct result of the injection.

Table 34. Non-ISR Adverse Events Occurring Within 1 Day After an Injection and Occurring at a Higher Frequency in Participants Receiving Injectable Cabotegravir, Injection Safety Population, Trial HPTN 083

Preferred Term	CAB N=2,117 n (%)	TDF/FTC N=2,081 n (%)	Risk Difference (95% CI)
Pyrexia	73 (3.4)	11 (0.5)	2.9 (2.1, 3.8)
Malaise	21 (1.0)	1 (0.05)	0.9 (0.5, 1.4)
Fatigue	29 (1.4)	11 (0.5)	0.8 (0.3, 1.4)
Chills	8 (0.4)	1 (0.05)	0.3 (0.1, 0.6)
Low density lipoprotein increased	62 (2.9)	28 (1.3)	1.6 (0.7, 2.5)
Blood glucose increased	112 (5.3)	79 (3.8)	1.5 (0.2, 2.8)
Blood cholesterol increased	44 (2.1)	22 (1.1)	1.0 (0.3, 1.8)

Source: adae.xpt; Software: R
Risk difference column shows difference (with 95% confidence interval) between treatment and comparator.
Abbreviations: CAB, cabotegravir; CI, confidence interval; ISR, injection site reaction; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 35. Non-ISR Adverse Events Occurring Within 7 Days After an Injection and Occurring at a Higher Frequency in Participants Receiving Injectable Cabotegravir, Injection Safety Population, Trial HPTN 083

Preferred Term	CAB N=2,117 n (%)	TDF/FTC N=2,081 n (%)	Risk Difference (95% CI)
Pyrexia	175 (8.3)	25 (1.2)	7.1 (5.8, 8.3)
Malaise	47 (2.2)	4 (0.2)	2.0 (1.4, 2.7)
Fatigue	54 (2.6)	19 (0.9)	1.6 (0.9, 2.4)
Chills	18 (0.9)	2 (0.1)	0.8 (0.3, 1.2)
Influenza like illness	18 (0.9)	4 (0.2)	0.7 (0.2, 1.1)
Myalgia	43 (2.0)	21 (1.0)	1.0 (0.3, 1.8)
Headache	132 (6.2)	98 (4.7)	1.5 (0.2, 2.9)
Dermatitis	7 (0.3)	0	0.3 (0.1, 0.6)
Hypertension	63 (3.0)	40 (1.9)	1.1 (0.1, 2.0)
Low density lipoprotein increased	62 (2.9)	29 (1.4)	1.5 (0.7, 2.4)
Blood cholesterol increased	46 (2.2)	23 (1.1)	1.1 (0.3, 1.8)

Source: adae.xpt; Software: R
Risk difference column shows difference (with 95% confidence interval) between treatment and comparator.
Abbreviations: CAB, cabotegravir; CI, confidence interval; ISR, injection site reaction; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Pyrexia events were further explored by comparing the rate of events within 7 days after injection and 8 or more days after injection. As shown in Table 36, pyrexia events were significantly more common in the CAB arm than the TDF/FTC arm in the 7-day period following an injection. However, in the period 8 or more days after an injection, there was no difference in the rate of pyrexia events between arms. To determine if there was a clear alternative etiology for participant's pyrexia AEs, we next identified the participants who experienced both a pyrexia (grouped query) AE and an infection AE within 7 days after an

injection. Among the nine subjects identified, none had pyrexia and infection AEs that overlapped in time. However, there were two subjects who had an infection AE (nasopharyngitis and rhinitis) starting 3 days after the end of the pyrexia AE. However, even if these two subjects were excluded from the analysis given a potential alternative etiology for pyrexia, the rate of pyrexia AEs within 7 days of an injection remains significantly higher in the CAB arm.

Table 36. Pyrexia Adverse Events ≤7 Days After Injection and >8 Days After Injection, Safety Population, Trial HPTN 083

Grouped Query Preferred Term	CAB N=2,117 n (%)	TDF/FTC N=2,081 n (%)	Risk Difference (95% CI)
Within 7 days of injection			
Pyrexia (GQ)	207 (9.8)	31 (1.5)	8.3 (6.9, 9.7)
Pyrexia	175 (8.3)	25 (1.2)	7.1 (5.8, 8.3)
Chills	18 (0.9)	2 (0.1)	0.8 (0.3, 1.2)
Influenza like illness	18 (0.9)	4 (0.2)	0.7 (0.2, 1.1)
Feeling hot	2 (0.09)	0	0.1 (-0.0, 0.2)
8 or more days after injection			
Pyrexia (GQ)	93 (4.4)	109 (5.2)	-0.8 (-2.1, 0.5)
Pyrexia	66 (3.1)	78 (3.7)	-0.6 (-1.7, 0.5)
Chills	3 (0.1)	4 (0.2)	-0.1 (-0.3, 0.2)
Influenza like illness	26 (1.2)	29 (1.4)	-0.2 (-0.9, 0.5)

Source: adae.xpt; Software: R
Risk difference column shows difference (with 95% confidence interval) between treatment and comparator.
Abbreviations: CAB, cabotegravir; CI, confidence interval; GQ, grouped query; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Lastly, given the findings suggesting that pyrexia may be a systemic response to injection and given that local injection reactions appear to decrease in frequency and intensity over time, we asked the Applicant to conduct an analysis of the incidence and intensity of postinjection pyrexia AEs over time. In an analysis submitted to the NDA on July 28, 2021, it appeared as though the frequency of postinjection pyrexia events in the CAB arm decreased over time (from 4% at Week 5 to <1% at Week 97). In addition, all postinjection pyrexia events were Grade 1 or 2 in severity, and there were no notable changes in the proportion of events that were Grade 1 versus Grade 2 over time.

HPTN 084

As was done for HPTN 083, we first conducted an analysis of pyrexia, sciatica, syncope, and musculoskeletal AEs occurring in Step 2 (regardless of the timing of the AEs relative to the timing of injection). As shown in Table 37, these PTs and group queries all occurred at a similar rate in both arms in Step 2 of HPTN 084.

Table 37. Potential Systemic Injection Reactions, Step 2, Safety Population, Trial HPTN 084

Reaction Type	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Musculoskeletal pain (GQ)	286 (18.8)	244 (16.1)	2.7 (0.0, 5.4)
Pyrexia (GQ)	55 (3.6)	55 (3.6)	-0.0 (-1.3, 1.3)
Sciatica (PT)	4 (0.3)	3 (0.2)	0.1 (-0.3, 0.4)
Syncope (PT)[1]	2 (0.1)	1 (0.07)	0.1 (-0.2, 0.3)

Source: adae.xpt; Software: R
[1] Though our analysis did not take into account the timing of the event compared to the most recent injection, the CSR notes that the two CAB syncope events occurred 9 and 58 days after the last injection, therefore not in the immediate postinjection period.
Group query Musculoskeletal pain contains: Musculoskeletal chest pain, Back pain, Arthralgia, Musculoskeletal pain, Pain in extremity, Neck pain, Arthritis, Myalgia, Muscle spasms, Muscle strain, Costochondritis, Flank pain, Musculoskeletal disorder, Osteoarthritis, Muscle tightness, Joint swelling, Groin pain, Joint stiffness, Tendonitis, Pain in jaw, Spinal osteoarthritis, Musculoskeletal discomfort, Bursitis, Torticollis, Joint effusion, Sacroiliitis
Group query Pyrexia contains: Influenza like illness, Feeling hot, Pyrexia, Chills
Risk difference column shows difference (with 95% confidence interval) between step 2 groups.
Abbreviations: CAB, cabotegravir; CI, confidence interval; GQ, grouped query; PT, preferred term; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

We next conducted analyses of all AEs occurring within 1 day after an injection and within 7 days after an injection among participants in the HPTN 084 injection safety population. Table 38 displays all non-ISR AEs that were reported within 1 day following an injection and that occurred at a higher frequency among participants in the CAB arm compared to the TDF/FTC arm. As shown, the only PTs meeting these criteria were PTs in the Investigations SOC. These PTs were more common in CAB participants throughout the trial (not just in the one day windows following injections) and do not seem to be a direct result of the injection itself. In addition, at the SOC level, events in the Musculoskeletal and connective tissue disorders SOC were more common among CAB participants, though all individual PTs in this SOC occurred at a similar frequency across arms. Our analysis of events occurring within 7 days after an injection revealed that the only event that occurred more frequently among CAB participants was blood glucose increased (data not shown).

Table 38. Non-ISR Adverse Events Occurring Within 1 Day After an Injection and Occurring at a Higher Frequency in Participants Receiving Injectable Cabotegravir, Injection Safety Population, Trial HPTN 084

System Organ Class Preferred Term	CAB N=1,519 n (%)	TDF/FTC N=1,516 n (%)	Risk Difference (95% CI)
Investigations (SOC)	1,331 (87.6)	1,297 (85.6)	2.1 (-0.4, 4.5)
Blood glucose increased (PT)	395 (26.0)	304 (20.1)	6.0 (3.0, 8.9)
Lipase increased (PT)	141 (9.3)	103 (6.8)	2.5 (0.6, 4.4)
Aspartate aminotransferase increased (PT)	146 (9.6)	112 (7.4)	2.2 (0.2, 4.2)
Musculoskeletal and connective tissue disorders (SOC)	30 (2.0)	14 (0.9)	1.1 (0.2, 1.9)

Source: adae.xpt; Software: R
Risk difference column shows difference (with 95% confidence interval) between treatment and comparator.
Recoding was performed as follows: Anogenital warts replaces: Papilloma viral infection
Abbreviations: CAB, cabotegravir; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, system organ class; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Given that there did not appear to be an increased frequency of pyrexia events among CAB participants in Step 2 overall, or in the periods within 1 or 7 days after an injection, no further pyrexia analyses were conducted for HPTN 084.

Conclusions

In summary, in HPTN 083 but not HPTN 084, there was an increased frequency of pyrexia events among CAB participants that was temporally associated with injections. Given this finding, the following section is included in Section 6 of the APRETUDE label:

Other Injection-Associated Adverse Reactions: In the HPTN 083 clinical trial, an increased incidence of pyrexia (including pyrexia, feeling hot, chills, influenza-like illness) (4%) was reported by participants receiving APRETUDE compared with participants receiving TRUVADA (<1%). There were no differences reported in the incidence of pyrexia between groups in HPTN 084.

7.6.3.2. Hypersensitivity Reactions and Rash

HSR

Serious or severe hypersensitivity adverse drug reactions have not been reported in association with CAB but have been reported in association with other drugs in the INSTI class. Drugs in the INSTI class have a WARNINGS and PRECAUTIONS for HSRs.

HPTN 083

A grouped query analysis of AEs potentially consistent with an HSR was conducted. As shown in Table 117 of the Appendix, the rate of overall HSRs (grouped query) as well as the rates of individual PTs associated with HSRs was similar across arms in both Step 1 and Step 2 of the trial (1.1% and 0.8% of CAB and TDF/FTC participants, respectively, experienced a HSR in Step 1; 5.3% and 4.6% of CAB and TDF/FTC participants, respectively, experienced a HSR in Step 2). There were two AEs included in the grouped query that were serious, though neither were considered study drug-related. These events are summarized below.

- Subject (b) (6): A 19-year-old male with no past medical history and no known allergies experienced an urticaria SAE on Study Day 234, 60 days after his most recent CAB injection. The skin findings were accompanied by fever. He was hospitalized and treated with methylprednisolone, hydroxyzine, desloratadine, and pantoprazole. Although no alternative etiology was identified, the event was not assessed to be study drug-related. There was no action taken with study drug and the event resolved.
- Subject (b) (6): A 22-year-old male had a Stevens Johnson Syndrome SAE that began on Study Day 117 and necessitated hospitalization. In addition to skin lesions, he had oral involvement and associated fever and tachycardia. The event was not assessed to be study drug-related as the event occurred 4 days after receiving a cosmetic injection and 56 days after his last CAB injection. There was no action taken with study drug and the SAE resolved.

Based on the timing of the above SAEs, this reviewer agrees with the investigators' assessments that the events are unlikely to have been study drug-related.

In addition, there were four participants who experienced nonserious Grade 3 'hypersensitivity' AEs in the CAB arm. None of these were assessed to be study drug-related and none led to discontinuation of study drug.

HPTN 084

A grouped query analysis revealed no imbalances in HSRs across arms in HPTN 084 (0.9% and 1.4% of CAB and TDF/FTC participants, respectively, experienced a HSR in Step 1; 4.2% and 4.4% of CAB and TDF/FTC participants, respectively, experienced a HSR in Step 2). Please see Table 118 for details. None of the hypersensitivity AEs were serious and only one led to treatment discontinuation and this occurred in a participant in the TDF/FTC arm. There were two hypersensitivity AEs among CAB participants that were assessed to be drug-related (a Grade 2 hypersensitivity AE and Grade 1 eosinophilia AE) compared to nine HSRs considered to be drug-related among TDF/FTC participants.

Conclusions

Across HPTN 083 and HPTN 084, there were no imbalances in HSRs. There were no serious or severe HSRs that were considered study drug-related among CAB participants. However, given the occurrence of severe/serious hypersensitivity ADRs in association with other INSTIs, the inclusion of Hypersensitivity Reactions in the WARNINGS and PRECAUTIONS section of the APRETUDE label is considered appropriate. This is consistent with the CABENUVA label which states, “Serious or severe hypersensitivity reactions have been reported in association with other integrase inhibitors and could occur with CABENUVA.”

Rash

In the CAB HIV-1 treatment program, rash events were common but were not serious and did not lead to treatment discontinuation. Therefore, rash was not included in the WARNINGS and PRECAUTIONS section of the CABENUVA label. However, other members of the INSTI drug class have been associated with serious rash events.

HPTN 083

A grouped query analysis of rash AEs generally revealed no imbalances between arms in Step 1 or Step 2 of the HPTN 083 (with the exception of the PT ‘Rash macular’ which was reported among 12 (0.6%) and 2 (0.1%) of CAB and TDV/FTC participants, respectively, during Step 2. Please see Table 117 for additional details regarding this grouped query analysis. None of the isolated rash events were serious, though rash AEs associated with systemic symptoms were not included in this analysis as they were included in the HSR analysis (as described above in the HSR section, there were two rash events associated with systemic symptoms (Urticaria and Stevens Johnson Syndrome) that were serious in nature). There were 4 (<1%) CAB participants and 3 (<1%) TDF/FTC participants with nonserious rash AEs that led to treatment discontinuation. Two of the CAB discontinuations due to a rash AE occurred in Step 1 (PTs rash and rash pruritic) and two occurred in Step 2 (PTs erythema, pruritus, and rash erythematous). In addition, there was an eczema AE that led to treatment discontinuation in a CAB participant in Step 1 (eczema was not included in the rash grouped query). For additional details of the rash events leading to discontinuation during Step 1, please see Section 7.7.2 on the optional OLI.

HPTN 084

In a grouped query analysis of rash events reported in HPTN 084, rash AEs were more common among participants in the CAB arm (Reported in 10.9% of CAB participants and 8.6% of TDF/FTC participants during Step 2). For a breakdown of individual rash PTs, please see Table 118 in the Appendix. None of the rash AEs were serious or led to study drug discontinuation. In a more limited rash analysis including only rash, erythema, pruritus, macular rash, papular rash, and maculopapular rash PTs, 2% of CAB participants and 1% of TDF/TFC participants experienced a rash AE that was assessed to be drug-related.

Conclusions

Rash events were common in both HPTN 083 and HPTN 084, though none were serious. Therefore, the review team has concluded that rash does not need to be included in the WARNINGS and PRECAUTIONS section of the APRETUDE label. However, based on the rate of drug-related rash AEs in HPTN 084, we recommend that rash be included in the table of common ADRs in Section 6 of the label.

7.6.3.3. Hepatobiliary Events

Hepatotoxicity (significant but asymptomatic elevation of ALT/AST) was identified as a potential safety issue early in the development program for CAB and CABENUVA has a WARNING and PRECAUTION for Hepatotoxicity. HPTN 083 and HPTN 084 both excluded persons with current or chronic history of liver disease, ALT ≥2 times the ULN, total bilirubin >2.5 times the ULN, hepatitis B virus surface antigen positive, or hepatitis C virus antibody positive.

HPTN 083

Liver AEs reported in HPTN 083 are summarized in Table 39. The proportion of participants experiencing drug-related AEs of ALT increased and drug-related liver-related AEs were higher in the TDF/FTC arm than in the CAB arm (as previously described, investigators were instructed to capture only Grade 2 and higher laboratory AEs). All other liver-related AEs occurred at a similar rate in both arms. There was one drug-induced liver injury AE reported in a CAB participant (Subject (b) (6)) during Step 2. This Grade 2, nonserious AE was reported in a 27-year-old male on Study Day 159. The verbatim term for the event was "hepatitis induced by recreational drugs" and accordingly, the event was not assessed to be study drug-related. There were no serious or fatal liver events among CAB participants.

Table 39. Liver Adverse Events Summary, Safety Population, Trial HPTN 083

Drug-Induced Liver Injury Assessment	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
AE grouping related to DILI	56 (2.5)	266 (12.6)	53 (2.3)	301 (14.5)	-1.9 (-4.0, 0.2)
Alanine aminotransferase increased	32 (1.4)	159 (7.5)	33 (1.4)	198 (9.5)	-2.0 (-3.7, -0.3)
Aspartate aminotransferase increased	34 (1.5)	185 (8.7)	31 (1.4)	197 (9.5)	-0.7 (-2.5, 1.0)
Bilirubin conjugated increased	1 (0.04)	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Drug-induced liver injury	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Hepatitis	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Hepatomegaly	1 (0.04)	0	0	0	0 (0, 0)
Maximum severity					
Death	0	0	0	0	0 (0, 0)
Life-threatening	4 (0.2)	10 (0.5)	2 (0.09)	21 (1.0)	-0.5 (-1.1, -0.0)
Severe	7 (0.3)	44 (2.1)	7 (0.3)	54 (2.6)	-0.5 (-1.4, 0.4)
Moderate	34 (1.5)	176 (8.3)	31 (1.4)	196 (9.4)	-1.1 (-2.8, 0.6)
Mild	11 (0.5)	36 (1.7)	13 (0.6)	30 (1.4)	0.3 (-0.5, 1.0)
Serious	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Deaths	0	0	0	0	0 (0, 0)
Resulting in discontinuation	7 (0.3)	24 (1.1)	3 (0.1)	28 (1.3)	-0.2 (-0.9, 0.5)
Relatedness	9 (0.4)	21 (1.0)	13 (0.6)	37 (1.8)	-0.8 (-1.5, -0.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE after the first dose of study drug and until 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively). For those with no injections, events after the first of 1 day after the date of discontinuation or 120 days after randomization were considered not treatment-emergent.
Duration is median 29 days for Step 1 groups and median 457 days for Step 2 groups.
Risk difference column shows difference (with 95% confidence interval) between step 2 groups.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; CAB, cabotegravir; CI, confidence interval; DILI, drug-induced liver injury; N, number of patients in treatment arm; n, number of patients with adverse event; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Laboratory results are presented in detail in Section 7.6.1.6. Increased ALT and total bilirubin values were more common among participants in the CAB arm compared to the TDF/FTC arm. The majority of the ALT and total bilirubin increases were Grade 1 and 2 abnormalities. Laboratory results were used to identify potential Hy's Law cases, defined as those with a maximum postbaseline total bilirubin equal to or exceeding 2x ULN within 30 days after maximum postbaseline ALT or AST equal to or exceeding 3x ULN, without findings of cholestasis (defined as alkaline phosphatase <2x ULN). The frequency of potential Hy's Law cases was balanced across arms (0.2% and 0.3% in the CAB and TDF/FTC arms). Of note, in addition to the five potential Hy's Law cases in the CAB arm identified in the CDS's original analysis, there were five additional potential Hy's Law cases in the CAB arm identified in additional analysis conducted by the CDS, the clinical reviewer, and the Applicant. It appears that the discrepancies in the Hy's Law analysis results were due to differences in the datasets used (ADLB versus ADLBHY) and differences in the specified time window for the various components of the Hy's Law definition to be assessed. Of the ten potential Hy's Law cases, eight participants had acute viral hepatitis at the time that Hy's Law criteria were met (hepatitis A, n=3; hepatitis B, n=3; hepatitis C, n=2). Among the remaining two potential Hy's Law cases without acute viral hepatitis to explain their liver function test abnormalities, one participant

(Subject [redacted] (b) (6)) met Hy's Law criteria based on AST but not ALT and had a concurrent Grade 4 CK elevation suggesting that muscle injury rather than liver injury may have driven the event; and the other participant (Subject [redacted] (b) (6)) had an ALT >3x the ULN (peak ALT of 168 IU/L) that was separated by approximately 4 weeks from the total bilirubin elevation and the laboratory abnormalities resolved despite ongoing study drug exposure.

None of the ten identified potential Hy's Law cases described above appear to be consistent with CAB-induced liver injury. Of note, an independent hepatic adjudication committee (HAC) reviewed all liver-related study drug discontinuations (N=78; 40 (1.8%) in the CAB arm and 38 (1.7%) in the TDF/FTC arm). The committee concluded that there were 14 (0.6%) and 15 (0.7%) participants in the CAB and TDF/FTC arms, respectively, who had probable or possible drug-induced liver injury. None of the participants that the review team identified as potential Hy's Law cases were assessed to have probable or possible drug-induced liver injury by the HAC (in many cases due to viral hepatitis serving as an alternative etiology for these liver-related events).

HPTN 084

Liver-related AEs reported in HPTN 084 are summarized in Table 40. As shown, the frequency of liver-related AEs was comparable across arms. There were no liver-related deaths and there was 1 liver-related SAE in each arm. The SAE reported in a CAB participant is summarized below.

- Subject [redacted] (b) (6): A 26-year-old woman was hospitalized on Study Day 55 for a Grade 4 'hepatitis acute' AE. The event was associated with Grade 4 ALT and bilirubin elevations. The SAE was assessed to be nonstudy drug-related; however, the event did lead to study drug discontinuation. Evaluation for acute viral hepatitis infection revealed a positive hepatitis A IgM. The event was also confounded by "excessive alcohol consumption" and use of an unspecified herbal medication.

Table 40. Liver Adverse Events Summary, Safety Population, Trial HPTN 084

Drug-Induced Liver Injury Assessment	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
AE grouping related to AESI	44 (2.7)	283 (18.6)	41 (2.5)	269 (17.7)	0.9 (-1.9, 3.6)
Alanine aminotransferase increased	28 (1.7)	219 (14.4)	29 (1.8)	217 (14.3)	0.1 (-2.4, 2.6)
Aspartate aminotransferase increased	27 (1.7)	196 (12.9)	20 (1.2)	170 (11.2)	1.7 (-0.6, 4.0)
Hepatitis acute	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Maximum severity					
Death	0	0	0	0	0 (0, 0)
Life-threatening	1 (0.06)	5 (0.3)	0	7 (0.5)	-0.1 (-0.6, 0.3)
Severe	1 (0.06)	13 (0.9)	2 (0.1)	11 (0.7)	0.1 (-0.5, 0.8)
Moderate	3 (0.2)	47 (3.1)	2 (0.1)	41 (2.7)	0.4 (-0.8, 1.6)
Mild	39 (2.4)	218 (14.4)	37 (2.3)	210 (13.9)	0.5 (-2.0, 3.0)
Serious	0	1 (0.07)	0	1 (0.07)	-0.0 (-0.2, 0.2)
Deaths	0	0	0	0	0 (0, 0)

Drug-Induced Liver Injury Assessment	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Resulting in discontinuation	3 (0.2)	10 (0.7)	2 (0.1)	13 (0.9)	-0.2 (-0.8, 0.4)
Relatedness	18 (1.1)	132 (8.7)	20 (1.2)	136 (9.0)	-0.3 (-2.3, 1.7)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE with an onset date on or after the start of treatment and before 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively).
Duration is median 29 days for Step 1 groups and median 452 days for Step 2 groups.
Risk difference column shows difference (with 95% confidence interval) between step 2 groups.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; CAB, cabotegravir; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Laboratory results are presented in detail in Section 7.6.2.6. Abnormalities in liver function test parameters were balanced across arms. Laboratory results were used to identify potential Hy's Law cases, as defined above. Our analysis revealed 1 potential Hy's Law case in the CAB arm and 2 in the TDF/FTC arm. The potential Hy's Law case in the CAB arm is summarized below. Of note, the Applicant's analysis also included subject (b) (6) (summarized above) as a potential Hy's law case.

- Subject (b) (6) A 28-year-old woman developed a Grade 4 ALT increase with an associated Grade 3 bilirubin elevation, abdominal pain, nausea, and vomiting. The event met serious criteria and led to study drug discontinuation. She was found to have a positive hepatitis A IgM and the event was attributed to acute hepatitis A infection. The event resolved.

The potential Hy's Law's cases in HPTN 084 are due to viral hepatitis and do not appear to represent CAB-induced liver disease. In addition to these cases identified in our review, the HAC reviewed 33 liver-related study drug discontinuations (15 (0.9%) in the CAB group and 18 (1.1%) om the TDF/FTC group). Of these, 8 (0.5%) and 7 (0.4%) of the events in the CAB and TDF/FTC groups, respectively, were concluded to represent probable or possible drug-induced liver injury.

Conclusions

None of the potential Hy's law cases identified in HPTN 083 or HPTN 084 appear likely to represent CAB-induced liver toxicity. Further, the proportion of participants experiencing a liver event that the HAC concluded was probably or possibly representative of drug-induced liver injury was balanced across arms. However, hepatoxicity has been observed with other INSTI drugs and with CAB+RPV use in HIV-1 treatment trials. Therefore, the review team agrees with the inclusion of a WARNINGS and PRECAUTIONS for hepatotoxicity in the APRETUDE label. Further, any grade ALT increased and AST increased laboratory abnormalities were common in both HPTN 083 and HPTN 084. The majority of the laboratory abnormalities were Grade 1 and 2 in severity. However, the rate of Grade 3 and 4 ALT and AST increased abnormalities was >1% in HPTN 083 and therefore ALT and AST abnormalities will be included in Section 6 of the APRETUDE label.

7.6.3.4. Psychiatric Events

Depressive disorders, including suicidal ideation or attempt, are labeled events for INSTIs. Both CABENUVA and VOCABRIA have a WARNINGS and PRECAUTIONS for depressive

disorders, specifically stating that "Depressive disorders (including depressed mood, depression, major depression, mood altered, mood swings, dysphoria, negative thoughts, suicidal ideation or attempt) have been reported."

HPTN 083

A "Mood disorder" grouped query analysis was conducted among participants in HPTN 083. As shown, the rate of mood disorder events was comparable among CAB and TDF/FTC. Similarly, the rate of mood disorder SAEs was balanced across arms (18 (<1%) and 20<1%) in the CAB and TDF/FTC arms, respectively). Lastly, treatment discontinuations due to mood disorder events were rare in both arms (7 (<1%) and 2 (<1%) in the CAB and TDF/FTC arms, respectively).

Table 41. Mood Disorders Grouped Query, Safety Population, HPTN 083

Grouped Query Preferred Term	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Mood disorder (GQ)	24 (1.1)	118 (5.6)	21 (0.9)	102 (4.9)	0.7 (-0.7, 2.0)
Major depression	0	11 (0.5)	2 (0.09)	3 (0.1)	0.4 (0.0, 0.7)
Depression	10 (0.4)	71 (3.4)	11 (0.5)	63 (3.0)	0.3 (-0.7, 1.4)
Irritability	5 (0.2)	6 (0.3)	1 (0.04)	2 (0.1)	0.2 (-0.1, 0.5)
Mood swings	1 (0.04)	4 (0.2)	3 (0.1)	2 (0.1)	0.1 (-0.1, 0.3)
Affect lability	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Affective disorder	1 (0.04)	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Depression suicidal	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Intentional self-injury	1 (0.04)	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Mood altered	1 (0.04)	1 (0.05)	0	2 (0.1)	-0.0 (-0.2, 0.1)
Suicidal ideation	2 (0.09)	14 (0.7)	2 (0.09)	14 (0.7)	-0.0 (-0.5, 0.5)
Suicide attempt	2 (0.09)	6 (0.3)	1 (0.04)	9 (0.4)	-0.1 (-0.5, 0.2)
Depressed mood	4 (0.2)	14 (0.7)	1 (0.04)	21 (1.0)	-0.3 (-0.9, 0.2)

Source: adae.xpt; Software: R
Abbreviations: CAB, cabotegravir; CI, confidence interval; GQ, grouped query; N, number of patients in treatment arm; n, number of patients with mood disorder; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

HPTN 084

A mood disorders grouped query analysis revealed a similar frequency of mood disorders among CAB and TDF/FTC participants. The most common mood disorder PT reported in both arms was depression. Two CAB participants and four TDF/FTC participants experienced one or more serious mood disorder events (SAEs reported among CAB participants were depression and intentional self-injury). Both of the SAEs reported in CAB participants occurred in the context of significant life stressors and neither were assessed to be study drug-related. Lastly, one CAB participant and no TDF/FTC participants discontinued study drug because of a mood disorder event. The AE that led to discontinuation in a CAB participant was suicidal ideation.

Table 42. Mood Disorders Grouped Query, Safety Population, Trial HPTN 084

Grouped Query	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Any GQ	219 (13.6)	811 (53.4)	236 (14.7)	786 (51.8)	1.5 (-2.0, 5.1)
Mood disorder (GQ)	0	9 (0.6)	2 (0.1)	13 (0.9)	-0.3 (-0.9, 0.3)
Mood swings	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Suicidal ideation	0	2 (0.1)	0	0	0.1 (-0.1, 0.3)
Depression	0	7 (0.5)	0	7 (0.5)	-0.0 (-0.5, 0.5)
Intentional self-injury	0	1 (0.07)	1 (0.06)	1 (0.07)	-0.0 (-0.2, 0.2)
Depressed mood	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Depression suicidal	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Depressive symptom	0	0	0	2 (0.1)	-0.1 (-0.3, 0.1)
Major depression	0	0	1 (0.06)	1 (0.07)	-0.1 (-0.2, 0.1)
Suicide attempt	0	0	0	2 (0.1)	-0.1 (-0.3, 0.1)

Source: adae.xpt; Software: R
Abbreviations: CAB, cabotegravir; CI, confidence interval; GQ, grouped query; N, number of patients in treatment arm; n, number of patients with mood disorder; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Conclusions

Mood disorder AEs including depression and suicidal ideation were reported in both HPTN 084 and HPTN 083 and were sometimes serious in nature. The frequency of these events was balanced across treatment arms in both trials. However, as TDF/FTC is labeled for depression, the observation that the rates of these events were similar among CAB and TDF/FTC participants could indicate that CAB is associated with an increased risk of mood disorder events. Therefore, the review team has concluded that the risk of depression should be included in the APRETUDE label. Given that this information is conveyed as a WARNING and PRECAUTION in both CABENUVA and VOCABRIA, a WARNING and PRECATUION is recommended for APRETUDE as well.

7.6.3.5. Neurologic Events

Neuropsychiatric events such as headache, sleep disorders, and dizziness are known AEs associated with the INSTI drug class. In addition, several “seizure-like” events were submitted as IND safety reports early in the course of the CAB for HIV-1 treatment development program. This led to seizures being evaluated as a potential risk associated with CAB use. A broad evaluation including all completed and ongoing trials of CAB for both HIV-1 treatment and prevention was undertaken at the time of the CABENUVA review. Upon the completion of this evaluation, the review team concluded that the incidence of seizures in the CAB development program was comparable to the general background rate of seizures, and therefore seizures were not included in the CABENUVA label.

HPTN 083

A summary of seizure AEs in HPTN 083 (combining Step 1 and 2 events) is presented in Table 43. The narratives for the three CAB participants experiencing seizure AEs were reviewed. One of the participants had a confirmed seizure 10 years prior, another had a possible prior seizure in childhood, and the remaining participant had no history of seizures but according to neurology his seizure AE was attributable to a recent increase in his Wellbutrin dose.

Table 43. Summary of Seizure Adverse Events, Safety Population, Steps 1 and 2 Combined, Trial HPTN 083

Adverse Event	CAB N=2,281 n (%)	TDF/FTC N=2,285 n (%)
Seizure AEs	3 (0.1)	5 (0.2)
Seizure	2 (<0.1)	5 (0.2)
Status epilepticus	1 (<0.1)	0
Seizure SAEs	3 (0.1)	1 (<0.1)
Seizure AEs leading to discontinuation	3 (0.1)	5 (0.2)
Drug-related seizure AEs	1 (<0.1)	3 (0.1)

Source: ADAE dataset, Analysis conducted in JMP version 15
Abbreviations: AE, adverse event; CAB, cabotegravir; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SAE, serious adverse event; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

HPTN 084

In HPTN 084, the only seizure AEs reported were one "seizure" in a TDF/FTC participant and one "psychogenic seizure" in a CAB participant. In addition, two CAB participants experienced nonserious syncope AEs. Neither syncope event was assessed to be study drug-related and no additional information was provided to suggest that these events represented seizures.

Conclusions

In conclusion, the results of HPTN 083 and HPTN 084 do not suggest that CAB is associated with an increased risk of seizures. No labeling for seizures is recommended.

7.6.3.6. Gastrointestinal Events and Pancreatitis

General Gastrointestinal Events

Gastrointestinal toxicity (mucosal inflammation) was observed in a single species (rats) in the CAB nonclinical program. In addition, in early clinical trials, there was a fatal gastrointestinal hemorrhage AE. Therefore, in the CABENUVA integrated review, a thorough assessment of gastrointestinal toxicity was undertaken. The majority of the gastrointestinal AEs reported in the CAB HIV-1 treatment program were found to be mild and nonserious; further the events occurred at a similar rate in the CAB+RPV group and the pooled control group. Therefore, gastrointestinal disorders (abdominal pain, gastritis, dyspepsia, vomiting, diarrhea, and flatulence) were included in the CABENUVA label as "Less Common Adverse Reactions."

HPTN 083

An analysis of FDA MedDRA queries (FMQs) under the Gastrointestinal disorders SOC revealed that gastrointestinal AEs (regardless of relatedness) generally occurred at a similar rate in CAB and TDF/FTC participants (with the exception of abdominal pain which was more common among CAB participants). Four CAB participants and six TDF/FTC participants experienced gastrointestinal SAEs. The SAEs reported by CAB participants were anal fissure, enteritis, hemorrhoids, and hemorrhoids thrombosed. Four CAB participants and three TDF/FTC participants discontinued study drug due to gastrointestinal AEs. Lastly, regarding relatedness, the following gastrointestinal ADRs occurred in at least 1% of CAB participants: diarrhea and

nausea (see Table 24 for additional details). These gastrointestinal ADRs occurred at a similar or higher rate in TDF/FTC participants.

Table 44. Adverse Events in Gastrointestinal Disorders System Organ Class by FDA Medical Query (Narrow), Safety Population, Trial HPTN 083

System Organ Class FMQ (Narrow)	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Gastrointestinal disorders (SOC)					
Abdominal pain	44 (1.9)	99 (4.7)	65 (2.8)	69 (3.3)	1.4 (0.2, 2.5)
Diarrhea	132 (5.8)	250 (11.8)	157 (6.9)	230 (11.1)	0.8 (-1.2, 2.7)
Dry mouth	6 (0.3)	11 (0.5)	4 (0.2)	3 (0.1)	0.4 (0.0, 0.7)
Vomiting	14 (0.6)	50 (2.4)	36 (1.6)	43 (2.1)	0.3 (-0.6, 1.2)
Dyspepsia	35 (1.5)	73 (3.4)	49 (2.1)	67 (3.2)	0.2 (-0.9, 1.3)
Pancreatitis	0	1 (0.05)	0	3 (0.1)	-0.1 (-0.3, 0.1)
Nausea	80 (3.5)	80 (3.8)	138 (6.0)	83 (4.0)	-0.2 (-1.4, 1.0)
Constipation	13 (0.6)	23 (1.1)	14 (0.6)	28 (1.3)	-0.3 (-0.9, 0.4)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE after the first dose of study drug and until 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively). For those with no injections, events after the first of 1 day after the date of discontinuation or 120 days after randomization were considered not treatment-emergent.
Duration is median 29 days for Step 1 groups and median 457 days for Step 2 groups.
Risk difference column shows difference (with 95% confidence interval) between step 2 groups.
Abbreviations: CAB, cabotegravir; CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

HPTN 084

As shown in Table 44, AEs (regardless of relatedness) in all FMQs under the Gastrointestinal disorders SOC occurred at a similar rate in CAB and TDF/FTC participants. No CAB participants experienced an SAE or an AE leading to treatment discontinuation under the Gastrointestinal disorders SOC. Lastly, gastrointestinal AEs were among the most common ADRs. The following gastrointestinal ADRs occurred in at least 2% of CAB participants: abdominal pain, diarrhea, vomiting, and nausea (see Table 30 for additional details). These gastrointestinal ADRs occurred at a similar or higher rate among TDF/FTC participants.

Table 45. Adverse Events in Gastrointestinal Disorders System Organ Class by FDA Medical Query (Narrow), Safety Population, Trial HPTN 084

System Organ Class FMQ (Narrow)	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Gastrointestinal disorders (SOC)					
Diarrhea	49 (3.0)	68 (4.5)	73 (4.5)	59 (3.9)	0.6 (-0.8, 2.0)
Dry mouth	1 (0.06)	1 (0.07)	2 (0.1)	0	0.1 (-0.1, 0.2)
Dyspepsia	8 (0.5)	78 (5.1)	28 (1.7)	77 (5.1)	0.1 (-1.5, 1.6)
Constipation	2 (0.1)	17 (1.1)	5 (0.3)	17 (1.1)	-0.0 (-0.8, 0.7)
Vomiting	18 (1.1)	32 (2.1)	58 (3.6)	38 (2.5)	-0.4 (-1.5, 0.7)
Abdominal pain	34 (2.1)	101 (6.6)	46 (2.9)	108 (7.1)	-0.5 (-2.3, 1.3)
Nausea	49 (3.0)	33 (2.2)	116 (7.2)	56 (3.7)	-1.5 (-2.7, -0.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE with an onset date on or after the start of treatment and before 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively).
Duration is median 29 days for Step 1 groups and median 452 days for Step 2 groups.
Risk difference column shows difference (with 95% confidence interval) between step 2 groups
Abbreviations: CAB, cabotegravir; CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Conclusions

In summary, gastrointestinal events such as diarrhea, nausea, and abdominal pain are among the most common (non-ISR) ADRs reported in HPTN 083 and HPTN 084. These events were typically nonserious and rarely lead to treatment discontinuations. Therefore, gastrointestinal ADRs will be included in the common ADR table in Section 6 of the ARETUDE label.

Pancreatitis

In the CAB+RPV phase 3b trial ATLAS-2M, there was a fatal acute pancreatitis AE. This AE was ultimately determined not to be treatment-related, and review of the complete data from the CAB+RPV HIV-1 treatment trials did not suggest an increased risk of pancreatitis in association with CAB+RPV. Therefore, no labeling for pancreatitis was recommended for CABENUVA.

HPTN 083

In HPTN 083, pancreatitis AEs were rare, occurring in 1 (<1%) CAB participant and 3 (<1%) TDF/FTC participants (plus one additional alcoholic pancreatitis AE in a TDF/FTC participant). The single pancreatitis AE in a CAB participant was Grade 2 in severity, nonserious, but was assessed to be treatment-related. In addition, abdominal pain AEs (FMQ) were reported in 4.7% of CAB participants and 3.3% of TDF/FTC participants during Step 2. These could have been representative of pancreatitis, however, none of these events were serious and none lead to treatment discontinuation. As shown in Section 7.6.1.6, Grade 3 and 4 lipase elevations occurred in approximately 3% of participants in both the CAB and TDF/FTC arms.

HPTN 084

There were no pancreatitis AEs reported in either arm in HPTN 084. As shown in Table 45, abdominal pain AEs occurred in a similar proportion of CAB and TDF/FTC participants. Lipase

elevations were reported in 11.8% of CAB participants and 10.2% of TDF/FTC participants. The majority of lipase elevations were Grade 1 or 2 in severity.

Conclusions

While mild and moderate lipase elevations were reported among CAB participants, there does not appear to be increased risk of symptomatic pancreatitis associated with CAB and no labeling for pancreatitis is needed.

7.6.3.7. Musculoskeletal Events Related to Injection or Rhabdomyolysis

Given the intramuscular route of administration, there was an interest in describing musculoskeletal events potentially related to CAB injections. As described in Section 7.6.3.1, the following potential temporal relationship between musculoskeletal events and CAB injections were identified: 1) increased rate of myalgia AEs within 7 days of an injection in the CAB arm compared to the TDF/FTC arm in HPTN 083, and 2) an increased rate of events in the Musculoskeletal disorders system organ class within 1 days of an injection in the CAB arm compared to the TDF/FTC arm in HPTN 084 (at the SOC level, but not for any particular PTs).

Other drugs in the INSTI class have been associated with myositis and CK elevations. Among HIV-infected participants in CAB+RPV trials, no rhabdomyolysis AEs were reported. However, nonserious, treatment-related muscle pain AEs (e.g., myositis, musculoskeletal pain, myositis) were reported in at least 2% of CAB+RPV participants (b) (4)

HPTN 083

In HPTN 083, a comprehensive grouped query analysis showed that there were no imbalances across arms in the rate of musculoskeletal events overall or for any individual PTs (see Table 117 for group query analysis). There were 14 participants (6 CAB participants and 8 TDF/FTC participants) who reported rhabdomyolysis AEs. Among the 6 CAB participants experiencing a rhabdomyolysis AE, none of them were considered treatment-related and one was serious and lead to treatment discontinuation. The rhabdomyolysis SAE is described briefly below.

- Subject (b) (6): A 27-year-old male developed rhabdomyolysis requiring hospitalization 34 days after receiving his first dose of CAB LA. The event occurred one day after lifting weights and working out. He had Grade 4 CK elevation (41,429 u/L). His CK values improved with hydration. The AE led to treatment discontinuation and was attributed to vigorous exercise and assessed as not related.

Myalgia AEs were common and occurred in a similar proportion of subjects in each arm (109 (5%) and 97 (4%) of CAB and TDF/FTC participants respectively). Drug-related myalgia AEs (i.e., ADRs) occurred in <1% of CAB participants. All myalgia AEs were Grade 1 and 2 in severity. There was also a single myositis AE reported during the trial and this occurred in a CAB participant. Lastly, as shown in Section 7.6.1.6, approximately one-third of participants in both arms experienced CK elevations, the majority of which, according to the Applicant's analysis, were asymptomatic.

HPTN 084

A grouped query analysis revealed that musculoskeletal pain AEs occurred in approximately 19% of participants in both arms during step 2. No participant in either arm reported a rhabdomyolysis or myositis AEs. However, myalgia AEs were reported in 55 (3.4%) CAB and 36 (2.2%) TDF/FTC participants. None of the myalgia events were serious and none led to treatment discontinuation. Nearly half of these myalgia AEs were assessed to be treatment related (myalgia ADRs were reported in 1.5% and 1.3% of CAB and TDF/FTC participants, respectively). Lastly, CK elevations were reported in 14.3% and 15.8% of CAB and TDF/FTC participants, respectively.

Conclusions

Based on the above findings, the review team finds that myalgia warrants inclusion in the label. Based on the frequency of drug-related myalgia events reported in HPTN 084 (but not HPTN 083), myalgia will be included in the common ADR table of the APRETUDE label. In addition, CK elevations will be included in the laboratory abnormalities section of the label. However, no labeling for rhabdomyolysis is indicated.

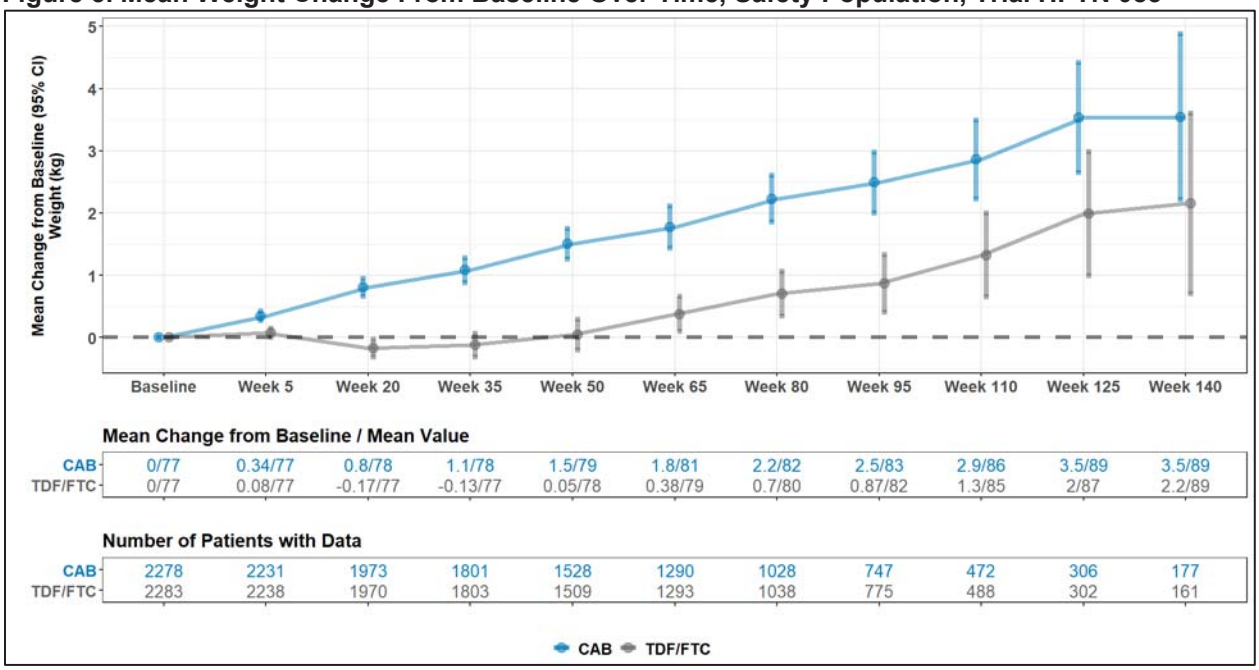
7.6.3.8. Weight Gain

Weight increase has been identified as an important risk associated with some members of the INSTI drug class. In the pivotal HIV-1 treatment trial ATLAS, participants in the CAB+RPV arm had a median weight increase of 1.8 kg, compared with a 0.3 kg weight gain in the control arm (which often would not have included an INSTI). There were no meaningful differences in cholesterol or glucose parameters between the CAB+RPV group and the control groups to suggest an associated increased risk for cardiovascular and metabolic events, though these analyses were thought to have been limited by the short (i.e., 48 weeks) duration of follow-up.

HPTN 083

As shown in Figure 5, participants in the CAB arm experienced greater weight gain over the course of the study than those participants in the TDF/FTC arm (though the mean weight increased over time in both arms). Further, a greater proportion of CAB participants experienced a weight increase ≥10% (15.7% and 10.6% in the CAB and TDF/FTC arms, respectively (risk difference (95% CI) =5.1 (3.1,7.0). There were no clear demographic characteristics that appeared to predispose CAB participants to weight gain ≥10%. Additionally, a comparison of plasma CAB concentration in those who did and did not experience a ≥10% weight gain revealed no differences.

Figure 5. Mean Weight Change From Baseline Over Time, Safety Population, Trial HPTN 083



Source: advs.xpt; Software: R
Time based on study day of measurement.
Abbreviations: CAB, cabotegravir; CI, confidence interval; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Further analyses were then conducted to ascertain whether CAB-associated weight gain is associated with metabolic sequelae. First, to assess for new onset diabetes and hyperglycemia, the rate of diabetes AEs and elevated fasting glucose laboratory abnormalities reported amongst those participants in each arm with and without a ≥10% weight gain were compared. Participants with diabetes at baseline were identified using the concomitant medication dataset (those who started a diabetes medication on or before the study start day and took the medication during the study) and these participants were excluded from these analyses. Next, an analysis was conducted to determine if CAB-associated weight gain led to new diagnoses of hyperlipidemia. The rates of fasting lipid abnormalities among participants in both arms with and without a ≥10% weight gain were compared in the subset of participants without baseline hyperlipidemia (i.e., those not taking a lipid-lowering medication at baseline).

Table 46. Diabetes Grouped Query, by Weight Category, Excluding Subjects With History of Diabetes, Trial HPTN 083

Group Query Preferred Term	CAB <10% Weight Incr N=1,904 n (%)	CAB ≥10% Weight Incr N=355 n (%)	TDF/FTC <10% Weight Incr N=2,026 n (%)	TDF/FTC ≥10% Weight Incr N=240 n (%)
Diabetes (GQ)	3 (0.2)	0	7 (0.3)	0
Diabetes mellitus (PT)	3 (0.2)	0	5 (0.2)	0
Type 2 diabetes mellitus	0	0	2 (0.1)	0

Source: adae.xpt, advs.xpt; Software: R
Subjects (n=41) excluded based on diabetes medications started on or before the study start and taken during the study.
Grouped query includes 'Diabetes mellitus', 'Type 2 diabetes mellitus', 'Diabetic ketoacidosis', and 'Diabetic metabolic decompensation.'
Abbreviations: CAB, cabotegravir; GQ, grouped query; Incr, increase; N, number of patients in treatment arm; n, number of patients meeting criteria; PT, preferred term; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 47. Elevated Fasting Glucose, by Weight Category, Excluding Subjects With History of Diabetes, Trial HPTN 083

Level	CAB <10% Weight Incr N=1,904 n (%)	CAB ≥10% Weight Incr N=355 n (%)	TDF/FTC <10% Weight Incr N=2,026 n (%)	TDF/FTC ≥10% Weight Incr N=240 n (%)
Glucose, high (mg/dL)				
Grade 2 (>125)	8/1023 (0.8)	7/317 (2.2)	19/1136 (1.7)	3/208 (1.4)
Grade 3 (>250)	1/1023 (0.1)	0/317 (0)	3/1136 (0.3)	0/208 (0)
Grade 4 (≥500)	0/1023 (0)	0/317 (0)	0/1136 (0)	0/208 (0)

Source: ad b.xpt, advs.xpt; Software: R
Subjects (n=41) excluded based on diabetes medications started on or before the study start and taken during the study.
In this table, level 1 corresponds to Division of AIDS (DAIDS) severity grading version 2.1 (2017) Grade 2 for fasting glucose. Level 2 corresponds to Grade 3 and level 3 corresponds to Grade 4.
The number of subjects with data is significantly lower than the number of subjects in the treatment group because fasting glucose was collected at weeks 57 and 105. At week 57, the number of CAB subjects remaining in the study was 1360 out of 2281, and the number of TDF/FTC subjects remaining was 1356 out of 2285.
Abbreviations: CAB, cabotegravir; Incr, increase; N, number of patients in treatment arm; n, number of patients meeting criteria; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 48. Elevated Fasting Lipids, by Weight Category, Excluding Subjects With History of Hyperlipidemia, Trial HPTN 083

Level	CAB <10% Weight Incr N=1889 n (%)	CAB ≥10% Weight Incr N=352 n (%)	TDF/FTC <10% Weight Incr N=2006 n (%)	TDF/FTC ≥10% Weight Incr N=238 n (%)
Cholesterol, total, high (mg/dL)				
Grade 2 (≥240)	59/1026 (5.8)	23/316 (7.3)	37/1137 (3.3)	7/207 (3.4)
Grade 3 (≥300)	5/1026 (0.5)	5/316 (1.6)	2/1137 (0.2)	1/207 (0.5)
LDL, high (mg/dL)				
Grade 2 (≥160)	73/1025 (7.1)	23/315 (7.3)	47/1137 (4.1)	8/207 (3.9)
Grade 3 (≥190)	24/1025 (2.3)	8/315 (2.5)	14/1137 (1.2)	1/207 (0.5)
Triglycerides, high (mg/dL)				
Grade 2 (>300)	28/1026 (2.7)	14/316 (4.4)	24/1137 (2.1)	8/207 (3.9)
Grade 3 (>500)	11/1026 (1.1)	5/316 (1.6)	5/1137 (0.4)	2/207 (1.0)
Grade 4 (>1000)	1/1026 (0.1)	1/316 (0.3)	2/1137 (0.2)	1/207 (0.5)

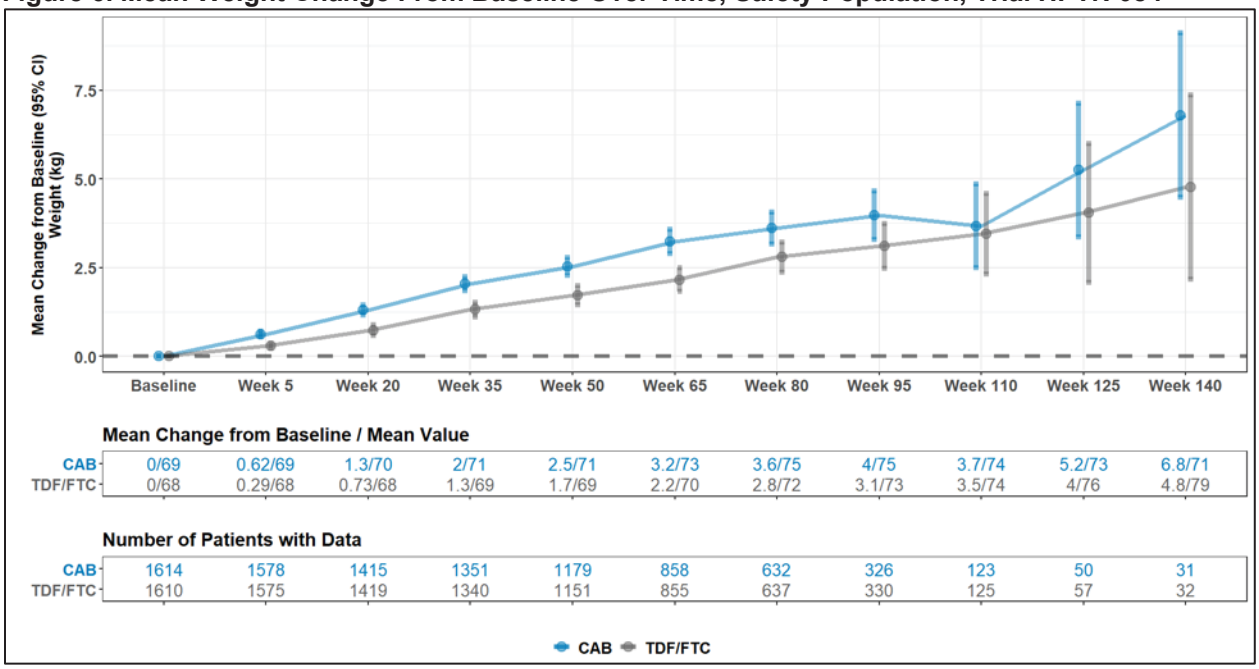
Source: ad b.xpt, advs.xpt; Software: R
Subjects (n=81) excluded based on lipid-lowering medications started on or before the study start and taken during the study.
In this table, level 1 corresponds to Division of AIDS (DAIDS) severity grading version 2.1 (2017) Grade 2 for fasting adults. Level 2 corresponds to Grade 3 and level 3 corresponds to Grade 4.
The number of subjects with data is significantly lower than the number of subjects in the treatment group because lipid data was collected at weeks 57 and 105. At week 57, the number of CAB subjects remaining in the study was 1360 out of 2281, and the number of TDF/FTC subjects remaining was 1356 out of 2285.
Abbreviations: CAB, cabotegravir; Incr, increase; LDL, low-density lipoprotein; N, number of patients in treatment arm; n, number of patients meeting criteria; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

As shown in Tables 46-48, diabetes AEs were uncommon overall and did not appear to increase in frequency among participants in either arm who had experienced ≥10% weight gain. Increased fasting glucose laboratory abnormalities were also uncommon, though the rate of Level 1 increased glucose events was higher among the CAB participants who had experienced ≥10% weight gain as compared to those CAB participants who had not (a similar trend was not observed in the TDF/FTC arm). Level 1 and 2 total cholesterol increased abnormalities and Level 1 triglyceride increased abnormalities were also more common among CAB participants who had experienced a ≥10% weight gain than those who had not. Similar trends were seen for triglycerides in the TDF/FTC arm, but not for total cholesterol.

HPTN 084

In HPTN 084, participants in the CAB arm experienced greater weight gain over the course of the study than those in the TDF/FTC arm, and the magnitude of weight gain was greater in both arms in HPTN 084 than it was in HPTN 083. A greater proportion of CAB participants also experienced a weight increase ≥10% (28.4% and 23.5% in the CAB and TDF/FTC arms, respectively (risk difference (95% CI) =4.9 (1.9,7.9)). As was seen in HPTN 083, there were no differences in baseline characteristics or in CAB exposures among those who did and did not have a ≥10% weight gain.

Figure 6. Mean Weight Change From Baseline Over Time, Safety Population, Trial HPTN 084



Source: advs.xpt; Software: R
Time based on study day of measurement.
Abbreviations: CAB, cabotegravir; CI, confidence interval; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Additional analyses were again conducted to ascertain whether CAB-associated weight gain was associated with metabolic sequelae. For these analyses, various metabolic parameters were compared in those participants who experienced ≥10% weight gain and those who experienced <10% weight gain. See the weight gain analyses description for HPTN 083 above for more information regarding methodology. Diabetes AEs were rarely reported among participants without a history of diabetes (based on reported use of drugs for the management of diabetes) and the events were evenly distributed across the ≥10% weight gain and <10% weight gain groups in both arms. Similarly, glucose and lipid elevations were rare, were almost exclusively Level 1 in severity, and did not occur with increased frequency among the subgroups with ≥10% weight gain.

Table 49. Diabetes Grouped Query, by Weight Category, Excluding Subjects With History of Diabetes, Trial HPTN 084

Group Query Preferred Term	CAB <10% Weight Incr N=1155 n (%)	CAB ≥10% Weight Incr N=459 n (%)	TDF/FTC <10% Weight Incr N=1231 n (%)	TDF/FTC ≥10% Weight Incr N=379 n (%)
Diabetes (GQ)	6 (0.5)	1 (0.2)	4 (0.3)	2 (0.5)
Diabetes mellitus	4 (0.3)	1 (0.2)	3 (0.2)	2 (0.5)
Type 2 diabetes mellitus	2 (0.2)	0	1 (0.08)	0
Diabetic ketoacidosis	1 (0.09)	0	0	0

Source: adae.xpt, advs.xpt; Software: R
Grouped query includes 'Diabetes mellitus', 'Type 2 diabetes mellitus', 'Diabetic ketoacidosis', and 'Diabetic metabolic decompensation.'
Abbreviations: CAB, cabotegravir; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 50. Elevated Fasting Glucose, by Weight Category, Excluding Subjects With History of Diabetes, Trial HPTN 084

Level	CAB <10% Weight Incr N=1155 n (%)	CAB ≥10% Weight Incr N=459 n (%)	TDF/FTC <10% Weight Incr N=1231 n (%)	TDF/FTC ≥10% Weight Incr N=379 n (%)
Glucose, high (mg/dL)				
Grade 2 (>125)	9/568 (1.6)	2/335 (0.6)	5/614 (0.8)	3/270 (1.1)
Grade 3 (>250)	0/568 (0)	0/335 (0)	1/614 (0.2)	0/270 (0)
Grade 4 (≥500)	0/568 (0)	0/335 (0)	0/614 (0)	0/270 (0)

Source: ad b.xpt, advs.xpt; Software: R
In this table, level 1 corresponds to Division of AIDS (DAIDS) severity grading version 2.1 (2017) Grade 2 for fasting glucose. Level 2 corresponds to Grade 3 and level 3 corresponds to Grade 4.
The number of subjects with data is significantly lower than the number of subjects in the treatment group because fasting glucose was collected at weeks 57 and 105, and some subjects had discontinued.
Abbreviations: CAB, cabotegravir; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 51. Elevated Fasting Lipids, by Weight Category, Excluding Subjects With History of Hyperlipidemia, Trial HPTN 084

Level	CAB <10% Weight Incr N=1155 n (%)	CAB ≥10% Weight Incr N=459 n (%)	TDF/FTC <10% Weight Incr N=1231 n (%)	TDF/FTC ≥10% Weight Incr N=379 n (%)
Cholesterol, total, high (mg/dL)				
Grade 2 (≥240)	4/598 (0.7)	2/356 (0.6)	2/652 (0.3)	1/287 (0.3)
Grade 3 (≥300)	0/598 (0)	0/356 (0)	0/652 (0)	0/287 (0)
LDL, high (mg/dL)				
Grade 2 (≥160)	8/598 (1.3)	7/356 (2.0)	5/652 (0.8)	2/287 (0.7)
Grade 3 (≥190)	1/598 (0.2)	0/356 (0)	1/652 (0.2)	0/287 (0)
Triglycerides, high (mg/dL)				
Grade 2 (>300)	1/598 (0.2)	0/356 (0)	1/652 (0.2)	1/287 (0.3)
Grade 3 (>500)	0/598 (0)	0/356 (0)	0/652 (0)	0/287 (0)
Grade 4 (>1000)	0/598 (0)	0/356 (0)	0/652 (0)	0/287 (0)

Source: ad b.xpt, advs.xpt; Software: R
In this table, level 1 corresponds to Division of AIDS (DAIDS) severity grading version 2.1 (2017) Grade 2 for fasting adults. Level 2 corresponds to Grade 3 and level 3 corresponds to Grade 4.
The number of subjects with data is significantly lower than the number of subjects in the treatment group because lipid data was collected at weeks 57 and 105, and some subjects had discontinued.
Abbreviations: CAB, cabotegravir; LDL, low-density lipoprotein; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Conclusions

In conclusion, CAB appears to be associated with greater weight increase over time than TDF/FTC. Further, this weight increase appears to be associated with low level increases in glucose and certain lipid parameters in HPTN 083. While these differences were relatively small across the study population, they may be of clinical significance on the individual patient level. Further, the impact of CAB on weight and metabolic parameters may increase with longer durations of use. Interestingly, these differences in glucose and lipid parameters based on weight gain category were not observed in HPTN 084, despite a greater magnitude of weight gain among participants in HPTN 084.

The potential negative effect of CAB on weight and metabolic parameters should be taken into consideration when patients and healthcare providers are choosing the optimal HIV-1 PrEP regimen for a given patient. As such, the observed weight gain in HPTN 083 and 084 will be described in Section 6 of the APRETUDE label. Further, lipid abnormalities will also be described in the label (though they will not be presented by <10% versus ≥10% weight gain).

7.6.3.9. Sexually Transmitted Infections

STIs have been identified as a potential safety signal in HIV-1 PrEP products. There is a theoretical concern that participants receiving HIV-1 PrEP have a false sense of security regarding HIV-1 protection that may result in an increase in high-risk sexual practices.

The rate of baseline STIs was very similar across arms in both trials. During the trials, all participants underwent routine screening for gonorrhea, chlamydia, syphilis, and hepatitis C virus infection at prespecified time points. In HPTN 083, STI testing was performed every 24 weeks after enrollment and in HPTN 084, STI tests were routinely performed at Week 33 and every 24 weeks thereafter. Both trials conducted hepatitis C virus testing at Week 57 and every 48 weeks thereafter. In addition, unplanned STI testing was performed in both trials when there was a suspected infection. As shown in Tables 52 and 53, STIs were common in both trials but there were no notable imbalances in the rate of STIs across arms. In addition, a grouped query analysis of all STI AEs was performed for each trial and also showed no imbalances between arms. Please see Tables 117 and 118 in the Appendices for additional details regarding the STI grouped query analyses.

Table 52. Incidence of Sexually Transmitted Infections, Safety Population, Trial HPTN 083

Sexually Transmitted Infection	CAB N=2281 n/N (%)	TDF/FTC N=2285 n/N (%)
Syphilis		
Participants infected among participants tested, n/N (%)	341/1860 (18)	337/1848 (18)
Positive tests among all tests performed, n/N (%)	448/5715 (8)	442/5712 (8)
Gonorrhea (urine)		
Participants infected among participants tested, n/N (%)	69/1829 (4)	49/1823 (3)
Positive tests among all tests performed, n/N (%)	74/5282 (1)	56/5231 (1)
Gonorrhea (rectal)		
Participants infected among participants tested, n/N (%)	240/1822 (13)	244/1818 (13)
Positive tests among all tests performed, n/N (%)	288/5218 (6)	285/5190 (5)
Chlamydia (urine)		
Participants infected among participants tested, n/N (%)	105/1829 (6)	115/1823 (6)
Positive tests among all tests performed, n/N (%)	115/5280 (2)	124/5232 (2)

Sexually Transmitted Infection	CAB N=2281 n/N (%)	TDF/FTC N=2285 n/N (%)
Chlamydia (rectal)		
Participants infected among participants tested, n/N (%)	322/1822 (18)	357/1818 (20)
Positive tests among all tests performed, n/N (%)	413/5227 (8)	453/5203 (9)
Hepatitis C		
Participants infected among participants tested, n/N (%)	7/1396 (<1)	11/1394 (<1)
Positive tests among all tests performed, n/N (%)	9/1991 (<1)	12/1995 (<1)

Source: admb dataset
Abbreviations: CAB, cabotegravir; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 53. Incidence of Sexually Transmitted Infections, Safety Population, Trial HPTN 084

Sexually Transmitted Infection	CAB N=1614 n/N (%)	TDF/FTC N=1610 n/N (%)
Syphilis		
Participants infected among participants tested, n/N (%)	18/1353 (1)	19/1345 (1)
Positive tests among all tests performed, n/N (%)	21/3069 (<1)	29/3034 (1)
Gonorrhea		
Participants infected among participants tested, n/N (%)	113/1358 (8)	123/1348 (9)
Positive tests among all tests performed, n/N (%)	121/3147 (4)	137/3115 (4)
Chlamydia		
Participants infected among participants tested, n/N (%)	265/1358 (20)	279/1348 (21)
Positive tests among all tests performed, n/N (%)	300/3147 (10)	339/3115 (11)
Trichomonas vaginalis		
Participants infected among participants tested, n/N (%)	148/1347 (11)	119/1338 (9)
Positive tests among all tests performed, n/N (%)	178/3098 (6)	144/3092 (5)
Hepatitis C		
Participants infected among participants tested, n/N (%)	5/1006 (<1)	4/1000 (<1)
Positive tests among all tests performed, n/N (%)	7/1140 (<1)	5/1134 (<1)

Source: admb dataset
Note: The same participant could be infected more than once, except for Hepatitis C.
Note: A participant was considered as diagnosed with active Syphilis if the non-Treponemal test result was reactive, the Treponemal test result was reactive/positive, and the titer was 1:8 or greater.
Note: A participant was considered as tested positive for Gonorrhea if test results for either Gonorrhea (urine) or Gonorrhea (vaginal swab) results were positive.
Note: A participant was considered as tested positive for Chlamydia if test results for either Chlamydia (urine) or Chlamydia (vaginal swab) results were positive.
Note: A participant was considered as tested positive for Trichomonas vaginalis if test results for either Trichomonas rapid test) or Trichomonas vaginalis (wet mount) results were positive.
Abbreviations: CAB, cabotegravir; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Reviewer comment: *The incident STI analyses presented above differ from the Applicant's incident STI analyses. The Applicant analyzed incident STIs in their efficacy assessments and therefore used the mITT population and did not limit their analyses to STIs that occurred while on blinded study product. Conversely, we considered STIs to be more pertinent to the evaluation of safety than efficacy. Therefore, our analyses were conducted in the safety population and are limited to events that occurred while on blinded study product (i.e., Steps 1 and 2). However, we acknowledge that differences in the rate of incident STIs across arms could indicate differences in sexual-risk behaviors and therefore differences in risk for HIV-1 acquisition, which could impact efficacy. As shown, the rates of STIs were very similar across arms suggesting that subjects in both arms were at similar risk for HIV-1 acquisition. For comparison, the Applicant's analyses (which include the incidence rate per 100 PY) are presented in Table 121 and Table 122.*

Given that HPTN 083 and HPTN 084 enrolled patients at high risk for HIV-1 infection, it is not surprising that STI's were common among study participants. The rates of STIs were found to be similar among those participants who received CAB and those who received TDF/FTC, suggesting both that CAB itself is not likely to be associated with an increased risk of STIs and that the arms remained well matched in terms of HIV-1 risk throughout the study.

Encouraging safer sex practices and performing regular testing for STIs are critical components of the management of individuals taking HIV-1 PrEP. As such, these practices will be recommended in the APRETUDE label as part of a WARNINGS and PRECAUTIONS on "Comprehensive Management to Reduce the Risk of HIV-1 Infection."

7.6.3.10. Pregnancy

Another INSTI, DTG, was considered to be potentially associated with embryo-fetal risk based in data from a prospective observational trial in Botswana (the Tsepamo study). As CAB and DTG have structural similarities, labeling based on structural similarity was included in Section 8.1 of the CABENUVA label.

HPTN 083

Not applicable.

HPTN 084

There were 38 participants in the CAB arm reporting 40 pregnancies and 34 participants in the TDF/FTC arm reporting 37 pregnancies. No congenital anomalies were reported. Please see Section 8.4 for additional information regarding the outcomes of these pregnancies.

In total, five participants reported AEs under the Pregnancy, puerperium and perinatal conditions SOC. The ruptured ectopic pregnancy and ectopic pregnancy events were SAEs. None of the events were assessed to be treatment related.

Table 54. Pregnancy Related Adverse Events, Safety Population, Trial HPTN 084

System Organ Class Preferred Term	CAB N=1614 n (%)	TDF/FTC N=1610 n (%)
Pregnancy, puerperium and perinatal conditions	2 (<1)	3 (<1)
Morning sickness	1 (<1)	1 (<1)
Ruptured ectopic pregnancy	0	1 (<1)
Ectopic pregnancy	1 (<1)	0
Abortion incomplete	0	1 (<1)

Source: ADAE
Analysis includes events that were treatment-emergent during Step 1 or Step 2.

Conclusions

There were no concerning findings regarding pregnancy outcomes or pregnancy-related AEs in HPTN 084. However, given the relatively small number of pregnancies, no definitive conclusions regarding the safety of CAB during pregnancy can be drawn. Given the potential association of DTG with neural tube defects and the structural similarity between DTG and RAL, the review team recommends the following text be included in Section 8 of the

APRETUDE label (similar to language currently included in the CABENUVA and VOCABRIA labels).

> There are insufficient human data on the use of APRETUDE during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage. While there are insufficient human data to assess the risk of neural tube defects (NTDs) with exposure to APRETUDE during pregnancy, NTDs were associated with dolutegravir, another integrase inhibitor. Healthcare providers should discuss the benefit-risk of using APRETUDE with individuals of childbearing potential or during pregnancy.
>
> Cabotegravir use in pregnant women has not been evaluated. APRETUDE should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

7.6.3.11. Neutropenia

Neutropenia was not identified as an AESI in the CABENUVA development program. Further, neutropenia is not a well-described safety concern for other members of the INSTI drug class. However, there were minor imbalances in neutropenia AEs and neutrophil count laboratory abnormalities across the CAB for HIV-1 PrEP program that prompted further exploration.

HPTN 083

The overall rate of neutropenia AEs was comparable across arms (0.7% and 0.8% in the CAB and TDF/FTC arms, respectively). Among these neutropenia AEs, only three were considered drug-related (two in the CAB arm and one in the TDF/FTC arm) and none led to permanent treatment discontinuation. Neutrophil decreased laboratory abnormalities (any grade) were more common among TDF/FTC participants than CAB participants (3.9% and 5.5% of CAB and TDF/FTC participants respectively).

HPTN 084

The overall rate of neutropenia events was higher among participants in the CAB arm (2.7% and 1.6% in the CAB and TDF/FTC arms, respectively). Similarly, there was a higher rate of treatment-related neutropenia AEs among CAB participants than TDF/FTC participants (2.0% and 1.1% in the CAB and TDF/FTC arms, respectively). The majority of the neutropenia AEs were Grade 1 and 2 in severity. Four CAB participants experienced Grade 3 neutropenia AEs and no CAB participants experienced a Grade 4 neutropenia AE. Among the four CAB participants with Grade 3 neutropenia AEs, all had Grade 3 neutrophil decreased laboratory abnormalities reported around the same time. None of the neutropenia AEs led to treatment discontinuation.

Additionally, a slightly higher proportion of CAB participants had any grade neutrophil count decreased laboratory abnormalities (6.4% and 5.6% in the CAB and TDF/FTC arms, respectively). Grade 3 and 4 neutrophil laboratory abnormalities were uncommon and relatively balanced across arms (0.4% and 0.2% in the CAB and TDF/FTC arms, respectively).

ÉCLAIR

In this phase 2 trial in HIV-uninfected men, 8 (7.6%) of CAB participants and 0 placebo participants experienced neutropenia clinical AEs. All of the neutropenia AEs were assessed to

be treatment related and three of the AEs led to treatment discontinuation. The neutropenia AEs that led to treatment discontinuation were Grade 2 (n=2) and Grade 3 (n=1) in severity. The three participants who discontinued treatment due to neutropenia AEs all had associated graded neutrophil laboratory abnormalities (Grade 1, Grade 2, and Grade 4). Overall, the proportion of participants experiencing an abnormal neutrophil count was similar across arms, though notably 1 (1.0%) CAB participant and 0 placebo participants had a Grade 4 neutrophil abnormality (see Section 17.7.2 for additional data).

According to the Applicant, "Of the subjects who developed a Grade 4 abnormal neutrophil count or AEs of white blood cell (WBC) count decreased, neutrophils decreased, or neutropenia, none had a current immune system disorder. None of the subjects had underlying neutropenia at Baseline and all abnormal events resolved."

HPTN 077

No concerning trends in neutropenia AEs or neutrophil count laboratory abnormalities were observed in this phase 2 trial.

Conclusions

An increased frequency in clinical neutropenia AEs among CAB LA subjects compared to TDF/FTC/placebo subjects was observed in some trials but not others. Notably, these neutropenia AEs led to treatment discontinuation in several participants in ÉCLAIR. Imbalances in neutrophil laboratory abnormalities were less pronounced if present at al. However, Grade 4 treatment-emergent neutrophil abnormalities were reported among a small number of CAB participants. Based on these findings, the review team concludes that routine postmarket pharmacovigilance is appropriate, and no labeling is indicated at this time.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Risk of Prolonged Exposures to CAB Monotherapy in Subjects who Become HIV-1 Infected

Issues

HIV-1 infections that are present before beginning antiretroviral-based pre-exposure prophylaxis, or that occur during the use of PrEP, may select for ARV-resistant virus. Moreover, these resistant viruses may be cross-resistant with other ARVs belonging to the same class, thereby limiting future treatment options. The selection of resistance by CAB, a member of the INSTI class of ARVs, could affect the efficacy of INSTI-based antiretroviral therapies, which comprise all the Department of Health and Human Services currently recommended initial regimens for most people with HIV-1.

Two issues have been identified that could contribute to prolonged exposure to CAB monotherapy in individuals who are unaware of being infected by HIV-1, an ideal situation for

selecting INSTI-resistant virus. The first issue is the observation of apparent "pharmacologic failures," HIV-1 infections that occur despite what is anticipated to be "adequate" CAB concentrations (based on the assumption that CAB trough concentration determined to be adequate when CAB/RPV LA is administered to HIV-1-infected patients will also be adequate to prevent HIV-1 acquisition with CAB LA monotherapy) and/or on-time injections. Thirty percent (6/20) of the HPTN 083 and HPTN 084 subjects who became infected while assigned to use CAB LA for PrEP were apparent pharmacologic failures. The second issue is that CAB use in individuals who are, or who become, infected may delay the time to HIV-1 diagnosis. Although the risk for delayed diagnosis of HIV-1 infection has been reported for currently approved PrEP products (e.g., Donnell and colleagues (Donnell et al. 2017)), the degree to which CAB affects the diagnosis of infection, both in terms of duration as well as in the types of assays that may be affected, is greater than what has been observed for the approved PrEP products, TRUVADA and DESCOVY.

Background

The Centers for Disease Control and Prevention reports PrEP is highly effective for preventing HIV-1 infection (Centers for Disease Control and Prevention 2021). Studies have shown that currently approved orally administered PrEP reduces the risk of acquiring HIV-1 from sex by approximately 99% when taken daily as prescribed.

Based on this prior PrEP experience, HIV-1 infection is not expected when there is a high rate of PrEP adherence. In the case of CAB, infections were not expected among participants with "adequate" plasma CAB exposures during the OLI and with on-time injections during Step 2. However, there were six subjects in HPTN 083, but no subjects in HPTN 084, who were diagnosed with HIV-1 infection while having achieved "adequate" drug concentrations during the OLI or despite on-time injections in Step 2 (to be referred to as "pharmacologic failures"). The target plasma drug concentrations are defined as ≥0.65 mcg/mL (≥1.6μM), which are equal to or greater than 4x the protein-adjusted 90% effective concentration (4x PA-IC_{90}) against a reference HIV-1 isolate in cell culture. This target concentration is based on the 5th percentile of C_{min} values in HIV-1 treatment trials in which CAB LA every 4 or 8 weeks in combination with RPV LA was shown to be effective in maintaining HIV-1 suppression in infected adults. However, the relationship between the ability of CAB, in combination with RPV, to maintain virologic suppression in people infected with HIV-1 and the potential for CAB LA monotherapy to prevent infection was (and remains) unclear. Furthermore, the most relevant site for predicting efficacy based on CAB concentrations may differ for HIV-1 prevention and treatment (e.g., anogenital tissue versus plasma). Nevertheless, considering that the dosing regimen approved for treatment and prevention of HIV-1 infection is the same for DESCOVY and TRUVADA, using the same target concentration of CAB for treatment and prevention (0.65 mcg/mL) was considered a reasonable estimate.

Assessment

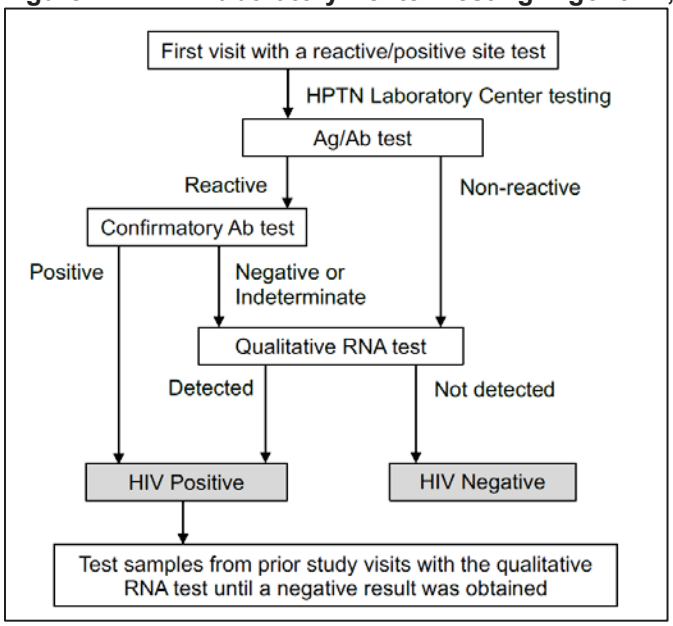
Diagnosis of HIV-1 Infections in HPTN 083 and HPTN 084

The HIV-1 testing algorithm used to identify infections in HPTN 083 and HPTN 084 is described by Marzinke and colleagues (Marzinke et al. 2021). Each study site used locally available tests that included at least one FDA-cleared rapid test and a laboratory-implemented

HIV-1 antibody/antigen (Ab/Ag) immunoassay. Some local sites also used the Gen-Probe Aptima® HIV-1 RNA Qualitative Assay (BL103966), a transcription-mediated amplification-based assay with a limit of detection of 30 copies/mL (c/mL), and/or a quantitative HIV-1 RNA assay, according to local standards. The identities of the rapid tests used in HPTN 083 were not recorded (confirmed in the Applicant's response dated November 3, 2021, to the information request communicated on October 20, 2021). The rapid tests used in HPTN 084 were primarily the OraSure OraQuick® ADVANCE Rapid HIV-1/2 Antibody Test (BP010047), the Alere/Abbott Determine™ HIV-1/2 rapid test (BP120037), or the Trinity Biotech Uni-Gold™ HIV-1/2 Rapid Test (BP030025).

Additional tests were conducted retrospectively by the HPTN Laboratory Center (Johns Hopkins University School of Medicine, Baltimore, MD) according to the algorithm illustrated in Figure 7 (Marzinke et al. 2021). The central laboratory's retrospective testing utilized the Abbott Architect® HIV Ag/Ab Combo assay (BP090080/0) and the Bio-Rad Geenius™ HIV-1/2 Supplemental Assay (BL125670) for confirmation. In addition, central laboratory evaluations used the Aptima HIV-1 RNA Qualitative Assay and the Abbott Real*Time* HIV-1 Viral Load Assay (BP060002), a reverse transcriptase polymerase chain reaction-based assay with a lower limit of quantification and limit of detection of 40 c/mL.

Figure 7. HPTN Laboratory Center Testing Algorithm, Trial HPTN 083



Source: Marzinke et al. (2021)
Abbreviations: Ab, antibody; Ag, antigen

HIV-1 genotyping was performed using the GenoSure PRIme® assay on blood samples with HIV-1 RNA ≥500 c/mL, which included 85% (17/20) of infected subjects who were assigned to use CAB LA and 94% (73/78) of infected subjects who were assigned to use TDF/FTC for prophylaxis. HIV-1 phenotyping using the Monogram PhenoSense® Integrase assay was attempted for samples from subjects in HPTN 083 but was successful only for isolates from 3 subjects. HIV-1 phenotyping was not performed for isolates from subjects in HPTN 084.

Infections Occurring in HPTN 083 and HPTN 084

There were 20 HIV-1 infections identified among subjects randomized to the CAB arms and 78 infections among subjects randomized to the TDF/FTC arms of HPTN 083 and HPTN 084 (Table 55). Most infections in HPTN 083 were associated with HIV-1 subtype B (66% [38/58]) and most infections in HPTN 084 with HIV-1 subtype C (80% [32/40]). The subtype distributions in the trials are consistent with the regions in which these infections occurred: for HPTN 083 primarily the United States (43% [25/58]) and Latin America (26% [15/58]), where HIV-1 subtype B is predominant; and for HPTN 084 primarily Southern Africa (95% [38/40]), where HIV-1 subtype C is predominant (Hemelaar et al. 2019).

Table 55. Overview of HIV-1 Infections and Resistance Assessments

	HPTN 083		HPTN 084		Pooled	
HIV-1 Infection/ Resistance Assessment	**CAB n (%)**	**TDF/FTC n (%)**	**CAB n (%)**	**TDF/FTC n (%)**	**CAB n (%)**	**TDF/FTC n (%)**
HIV-1 infections[1]	16	42	4	36	20	78
Prevalent	4 (25)	3 (7)	1 (25)		5 (25)	3 (4)
Incident	12 (75)	39 (93)	3 (75)	36 (100)	15 (75)	75 (96)
HIV-1 subtypes						
A1			1	2	1	2
A/B	1 (6)				1 (5)	
A/C				1 (3)		1 (1)
AE	1 (6)	3 (7)			1 (5)	3 (4)
AG		1 (2)				1 (1)
B	7 (44)	31 (74)			7 (35)	31 (40)
BC		1 (2)				1 (1)
BF	2 (13)	1 (2)			2 (10)	1 (1)
C	2 (13)	2 (5)	3 (75)	29 (81)	5 (25)	31 (40)
C/K				1 (3)		1 (1)
F1		1 (2)				1 (1)
Missing	3 (19)	2 (5)		3 (8)	3 (15)	5 (6)
Resistance data						
Genotypic	13 (81)	40 (95)	4 (100)	33 (92)	17 (85)	73 (94)
Phenotypic	3 (19)				3 (15)	

Source: Supplemental Virology Report (201738 / HPTN 083); Supplemental Virology Report (201739 / HPTN 084); pf.xpt (HPTN 083 supplemental); pf.xpt (HPTN 084 supplemental); Software: JMP 15; Excel 365
[1] Virology analyses included subjects with prevalent infections who were undiagnosed at enrollment and incidental infections that occurred while subjects were scheduled to receive randomized prophylaxis.
Abbreviations: CAB, cabotegravir; TDF/FTC, emtricitabine/tenofovir disoproxil fumarate; HIV-1, human immunodeficiency virus type 1

A summary of key information for the HIV-1 infections that occurred among subjects randomized to receive CAB for PrEP is presented in Table 56, with additional data provided in Table 133. Subjects in HPTN 083 were also classified by the Applicant based on the relationship between the timing of HIV-1 diagnosis and exposure to study drug and assigned a blinded ID code. The categories include: (A) infections diagnosed at baseline (i.e., prevalent infections), (B) infections that occurred during a period with no recent CAB exposures (e.g., the last CAB LA injection occurred ≥6 months before the earliest HIV-1 diagnosis), (C) infections diagnosed during the OLI period, and (D) infections diagnosed in the setting of on-time CAB LA injections. Table 56 also provides the day that each CAB LA injection was administered, the earliest day that HIV-1 infection was diagnosed by the local study site, the earliest day that HIV-1 infection was diagnosed retrospectively by the central laboratory, and the plasma CAB concentrations, plasma viral load data, and genotypic resistance data using samples collected at

the indicated time points. The time points shown in Table 56 include the days of HIV-1-infection diagnoses by the local site and central laboratory, as well as any time point with genotypic resistance data. Plasma CAB concentrations and HIV-1 diagnostic data for all assessed time points are shown in Table 133.

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Table 56. Summary of HIV-1 Infections in CAB Arms, Trials HPTN 083 and HPTN 084

			HIV-1 Detection[2]		Plasma CAB Concentrations and Virology Data			
Trial	Subject (Code)[1]	CAB-LA Injection (Day)	Local Site (Day)	Central Lab (Day)	Sample (Day)	[CAB][3] (mcg/mL)	HIV-1 RNA[4] (c/mL)	INSTI RAS[5]
Infections diagnosed at baseline (i.e., prevalent infections)								
HPTN083	[redacted] (A1)	None	29	1	1	<0.025	4,010	WT
					29	3.228	78	
HPTN083	[redacted] (A4)	39, 64	64	1	1	<0.025	44,180	WT
					64	2.997		
HPTN083	[redacted] (A3)	36, 66	73	1	1	<0.025	1,360	WT
					73	5.428		
					186	0.586	1,440	WT
					249	0.056	76,090	WT
HPTN083	[redacted] (A2)	41	61	1	1	<0.025	50,080	WT
					20	11.950	20,760	WT
					30	4.274	700	WT
					61	3.840	1,660	E138K, Q148K
					70	2.533	4,829	E138K, Q148K
HPTN084	[redacted]	33, 60, 114, 173, 227	227	1	1	<0.025	<40	
					15	6.958	500	WT
					26	0.147	1,740	WT
					33	<0.025	6,300	WT
					227	2.581		
Infections that occurred during a period with no recent CAB exposures/Low plasma CAB concentrations								
HPTN083	[redacted] (b) (6) (B4)	37, 62, 120	401	401	401	<0.025	770	
HPTN083	[redacted] (b) (6) (B5)	None	350	350	350	<0.025	2,559	WT
HPTN083	[redacted] (b) (6) (B1)	39, 108	957	957	957	0.065	65,530	WT
HPTN083	[redacted] (b) (6) (B2)	None	725	725	725	<0.025	53,220	WT
HPTN083	[redacted] (b) (6) (B3)	36, 80, 128, 176	393	393	393	0.100	50,440	WT
HPTN084	[redacted] (b) (6)	None	402	402	402	<0.025	42,810	WT
					535	<0.025	44,870	WT
HPTN084	[redacted]	None	77	77	77	<0.025	26,840	WT

Trial	Subject (Code)[1]	CAB-LA Injection (Day)	HIV-1 Detection[2] Local Site (Day)	HIV-1 Detection[2] Central Lab (Day)	Plasma CAB Concentrations and Virology Data Sample (Day)	[CAB][3] (mcg/mL)	HIV-1 RNA[4] (c/mL)	INSTI RAS[5]
HPTN084	(b) (6)	39, 79, 109, 169, 211, 317, 351, 409, 522	522	522	522	0.416	875,200	WT
					526	1.217	3,927,990	WT
Infections detected during the oral CAB lead-in								
HPTN083	(b) (6) (C1)	37, 65	75	28	28	6.301	120	
					65	1.841	2,174	L74I, Q148R, E157Q
					75	3.469	1,373	L74I, E138E/K, G140G/S, Q148R, E157Q
HPTN083	(b) (6) (C3)	35	55	20	20	10.690	ND	
					55	1.108	102,329	E138A, Q148R
					56	1.182	218,776	E138A, Q148R
HPTN083	(b) (6) (C2)	None	232	47	47	<0.025	494	
					232	<0.025	229,810	WT
					233	2.559	207,810	WT
Infections detected during target CAB concentrations/in the setting of on-time CAB LA injections								
HPTN083	(b) (6) (D4)	36, 64, 120, 178	178	133	133	2.017	<40	
					178	1.930	158	
					274	2.261	152,730	G140A, Q148R
HPTN083	(b) (6) (D3)	37, 64, 120, 182, 232	237	120	120	1.504	860	WT
					232	1.220	7,160	R263K
					237	1.645	5,510	R263K
HPTN083	(b) (6) (D2)	36, 64, 120, 176, 232, 288	288	190	190	1.405	ND	
					288	1.795		
HPTN083	(b) (6) (D1)	34, 62, 118, 174, 225, 300, 337, 393, 449, 505	505	393	393	1.613	130	
					505	1.444	<40	

Source: Supplemental Virology Report (201738 / HPTN 083); Supplemental Virology Report (201739 / HPTN 084); ex.xpt, mb.xpt, pc.xpt, pf.xpt (HPTN 083 supplemental); ex.xpt, mb.xpt, pc.xpt (HPTN 084), pf.xpt (HPTN 084 supplemental); Software: JMP 15; Excel 365

[1] Applicant-assigned code for subjects shown in parenthesis.
[2] Earliest day of HIV-1 diagnosis at the local study site in real-time or by the central laboratory's retrospective analysis.
[3] Plasma CAB concentration. Lower limit of quantification =0.025 mcg/mL.
[4] HIV-1 RNA as detected by a quantitative RT-PCR assay (HIV-1 RNA copies/mL). <40 c/mL = HIV-1 RNA detected but below the assay's lower limit of quantification; ND = HIV-1 RNA not detected.
[5] INSTI resistance-associated substitutions
Abbreviations: c/mL, copies/mL; CAB, cabotegravir; HIV-1, human immunodeficiency virus type 1; ND, not detected; RAS, resistance-associated substitution; WT, wild-type (i.e., absence of major INSTI resistance-associated substitutions)

Pharmacologic Failures

Six subjects from HPTN 083 represent potential pharmacologic failures. These include Subjects [redacted] (D4), [redacted] (D3), [redacted] (D2), and [redacted] (D1), who became infected despite receiving the scheduled CAB LA injections, and Subjects [redacted] (C1) and [redacted] (C3), who became infected during the OLI despite having achieved target plasma CAB concentrations ≥0.65 mcg/mL at the time of diagnosis.

- HPTN 083 Subject [redacted] (D4) is from South Africa and infected by HIV-1 subtype C. CAB LA injections were administered on Days 36, 64, 120, and 178. Infection was detected by the local site's Ag/Ab test on Day 178, when the plasma CAB concentration was 1.930 mcg/mL, and retrospectively by the central laboratory's qualitative and quantitative RNA assays on Day 133, when the plasma CAB concentration was 2.017 mcg/mL. The last negative diagnosis was on Day 120, when the plasma CAB concentration was 1.369 mcg/mL. Interestingly, CAB plasma concentrations were ≤0.65 mcg/mL, at 0.389 mcg/mL and 0.305 mcg/mL on Days 43 and 64, respectively, despite receiving a CAB LA injection on Day 36. This subject's BMI at baseline was 27.8 and no STIs (chlamydia, gonorrhea, or syphilis) were reported. This subject replied affirmatively when queried about injection drug use (IDU) at the time of the local site's confirmed HIV-1 infection visit.
- HPTN 083 Subject [redacted] (D3) is from Latin America and infected by HIV-1 subtype B/F. CAB LA injections were administered on Days 37, 64, 120, 182, and 232. Infection was detected by the local site's rapid test on Day 237 (an indeterminant result was produced for the Ag/Ab assay on Day 232), when the plasma CAB concentration was 1.645 mcg/mL, and retrospectively by the central laboratory's qualitative and quantitative RNA assays, but not the Ag/Ab assay, on Day 120, when the plasma CAB concentration was 1.504 mcg/mL. The plasma CAB concentration at the last HIV-1 negative visit (Day 76) was 3.046 mcg/mL. This subject's BMI at baseline was 31.1 and no STIs (chlamydia, gonorrhea, or syphilis) or history of IDU were reported, although an AE of cervix warts was reported on Day 31.
- HPTN 083 Subject [redacted] (D2) is from Latin America and infected by HIV-1 of an unknown subtype. CAB LA injections were administered on Days 36, 64, 120, 176, 232, and 288. Infection was detected by the local site's Ag/Ab assay on Day 288, when the plasma CAB concentration was 1.795 mcg/mL, and by the central laboratory's qualitative RNA, but not by the Ag/Ab or quantitative RNA assay, on Day 190, when the plasma CAB concentration was 1.405 mcg/mL. The plasma CAB concentration was 1.353 mcg/mL at the last HIV-1 negative visit (Day 176). This subject's BMI at baseline was 25.6 and no STIs (chlamydia, gonorrhea, or syphilis) or history of IDU were reported.
- HPTN 083 Subject [redacted] (D1) is from the United States and infected by HIV-1 of an unknown subtype. CAB LA injections were administered on Days 34, 62, 118, 174, 225, 300, 337, 393, 449, and 505. Infection was detected by the local site's Ag/Ab test on Day 505, when the plasma CAB concentration was 1.444 mcg/mL, and by the central laboratory's qualitative and quantitative RNA assays Day 393, when the plasma CAB concentration was 1.613 mcg/mL. The plasma CAB concentration at the last HIV-1 negative visit (Day 351) was 2.320 mcg/mL. This subject's BMI at baseline was 33.9.

Chlamydia and syphilis were reported as AEs on Day 225, chlamydia and gonorrhea on Day 510, syphilis on Day 524, and chlamydia on Day 627. No history of IDU was reported.

- HPTN 083 Subject (b) (6) (C1) is from Latin America and infected by HIV-1 subtype B. Infection was detected by the local site on Day 75 and retrospectively by the central laboratory on Day 28. CAB LA injections were administered on Days 37 and 65. Plasma CAB concentrations were 6.301 mcg/mL at the earliest HIV-1 diagnosis (Day 28) and 4.013 mcg/mL at the preceding visit (Day 17). This subject's BMI at baseline was 22.8 and no STIs (chlamydia, gonorrhea, or syphilis) or history of IDU were reported.
- HPTN 083 Subject (b) (6) (C3) is from Latin America and infected by HIV-1 subtype B. A CAB LA injection was administered on Day 35. Infection was detected by the local site's rapid tests and Ag/Ab assay on Day 55, when the plasma CAB concentration was 1.108 mcg/mL, and by the central laboratory's qualitative RNA assay on Day 20, when the plasma CAB concentration was 10.690 mcg/mL. This subject's BMI at baseline was 27.8 and no STIs (chlamydia, gonorrhea, or syphilis) were reported as AEs. No history of IDU was reported.

There were no pharmacologic failures reported in HPTN 084. One theoretical explanation for the apparent disparity between HPTN 083 and HPTN 084 is that there is a difference in tissue CAB concentrations at the site of HIV-1 exposure, e.g., CAB plasma concentrations are higher in females than in MSM, CAB concentrations are higher in cervical/vaginal tissues than in rectal tissue. There are limited animal data indicating that tissue concentrations following a single 400 mg IM dose of CAB are higher in cervical (0.13 mcg/mL) and vaginal (0.18 mcg/mL) tissue than in rectal tissue (0.06 mcg/mL). However, it is difficult to discern whether there are differences between CAB concentrations in cervical/vaginal and rectal tissues in humans due to high variability. In any case, this remains a theoretical consideration in the absence of tissue concentration data from clinical trials and without a clear understanding of the target tissue concentrations that are critical for effective HIV-1 prophylaxis.

It is possible that some of these breakthrough infections can be attributed to the acquisition of a virus with pre-existing INSTI resistance, although none of these six cases demonstrate such an event clearly. No resistance data were collected successfully from Subjects (b) (6) (D2) or (b) (6) (D1), while Subject (b) (6) (D3) had wild-type virus detected before an R263K-expressing variant emerged. The first two of these cases are not informative, while the third indicates the likely acquisition of wild-type virus followed by the emergence of a CAB-selected INSTI-resistant variant.

The three remaining cases are ambiguous, with viruses detected while plasma HIV-1 RNA concentrations were too low for resistance analyses. Viruses expressing one or more INSTI resistance-associated substitutions (RAS) were detected at later time points after plasma HIV-1 RNA levels had increased. Subject (b) (6) (C1) had an uncharacterized virus detected on Day 28 and a virus expressing INSTI RAS on Day 65 (L74I+Q148R+E157Q) that accumulated additional RAS by Day 75 (E138K+G140S). Subject (b) (6) (C3) had an uncharacterized virus detected on Day 20 followed by a virus expressing INSTI RAS (E138A+Q148R) detected on Day 55. Subject (b) (6) (D4) had uncharacterized virus detected on Days 133 and 178 followed by high levels of an INSTI RAS (G140A+Q148R)-expressing variant detected on Day 274. In these cases, it is unclear whether the early low-level viremia was associated with wild-

type virus unable to replicate efficiently in the presence of CAB monotherapy or INSTI-resistant virus detected very early during the infection.

Various additional analyses were conducted to identify factors that could have contributed to the occurrence of pharmacologic failures in the six HPTN 083 participants. Five of the six pharmacologic failures were MSM and the remaining pharmacologic failure was a transgender woman. The pharmacologic failures occurred at clinical sites across the United States, South America, and Africa. There were no clear trends in BMI to explain the pharmacologic failure (the mean BMI of the six pharmacologic failures was 28.2, compared to a mean BMI of the overall CAB arm of 25.5). Consideration was also given to the possibility that these participants may have been exposed to a large HIV-1 inoculum by IDU (despite IDU being an exclusion criterion). However, based in the limited data collected regarding IDU, it appears that only one of the pharmacologic failures (D4) reported a history of recent IDU during the trial. Lastly, the potential for recent STIs to have increased these participants' susceptibility to HIV-1 acquisition was explored. One of the six pharmacologic failures (D1) was found to have been diagnosed with an STI (chlamydia and syphilis) prior to HIV-1 infection. None of the assessed factors (BMI, STIs, IDU) were shared by these subjects, indicating that there might be multiple factors that can lead to CAB LA prophylaxis failures. It is also possible that at least some of these subjects were within the eclipse phase of acute HIV-1 infection at baseline and that virologic suppression by CAB monotherapy delayed successful diagnosis.

Delay in HIV-1 Diagnosis

The use of ARV-based PrEP products by HIV-1-infected individuals may affect the ability of HIV-1 diagnostic assays to detect infection (Donnell et al. 2017), a delay that is likely due to suppressed viral replication, which reduces the viral analytes targeted by some diagnostic assays, and an increase in the time required for the development of the high-affinity anti-HIV-1 antibodies required for detection by other assays (Parker et al. 2021).

Marzinke and colleagues (Marzinke et al. 2021) reported that subjects in HPTN 083 who were assigned to the CAB arm and became infected experienced such a delay, with 69% (11/16) of cases in the CAB arm and 24% (10/42) in the TDF/FTC arm demonstrating at least one study visit where the local site failed to detect an infection. When expanding the analysis to include HPTN 084, 60% (12/20) of cases in the CAB arms and 23% (18/77) of cases in the TDF/FTC arms had a delay of 1 or more visits before the local site detected HIV-1 infection relative to the retrospective testing by the central laboratory. Among those subjects who experienced a delayed diagnosis by their local site, the duration of the delay was also greater in the CAB arm than in the TDF/FTC arm. The median (interquartile range (IQR)) number of days between diagnosis of HIV-1 infection at the central and local laboratories was 67.5 (IQR: 45.5 to 115.75) days in the CAB arm and 34.5 (IQR: 21.25 to 58) days in the TDF/FTC arm. Similarly, the median (IQR) number of visits before the local site detected infection among the delayed cases was 4 (IQR: 2.25 to 5) in the CAB arm and 1 (IQR: 1 to 2) in the TDF/FTC arm. The greater delays observed for CAB than TDF/FTC may be attributable to greater antiviral activity and durability of CAB relative to TDF/FTC and/or to more consistent exposures due to improved product adherence.

The results of the diagnostic assays run for subjects in the CAB LA who experienced delayed diagnoses at the local site are shown in Table 57, which shows data for the time points spanning from the earliest central laboratory HIV-1 diagnosis to the earliest local site diagnosis. Notably, delayed diagnosis was experienced by the five subjects with prevalent infections, the six

pharmacologic failures, and HPTN 084 Subject [redacted] (b) (6) With the exceptions of HPTN 083 Subject [redacted] (b) (6) (C2) and HPTN 084 Subject [redacted] (b) (6) these subjects had plasma CAB concentrations that were ≥0.65 mcg/mL for each postbaseline visit during the period that the local site laboratories failed to detect the infection. Subject [redacted] (b) (6) (C2) had no quantifiable levels of plasma CAB until Day 233, while HPTN 084 Subject [redacted] (b) (6)'s plasma CAB concentrations fell below 0.65 mcg/mL from Day 26 through Day 38. The periods of delayed diagnoses were also often characterized by periods of low viral loads likely attributable to the antiviral activity of CAB monotherapy.

Table 57. HIV-1 Diagnostic Assays for HIV-1-infected Subjects in CAB Arms

			Site Diagnostics						Central Diagnostics			
			Rapid Tests		Ag/Ab Tests		HIV-1 RNA[4]				HIV-1 RNA[4]	
Subject (Code)[1]	Day[2]	CAB (mcg/mL)[3]	1	2	1	2	Qual	(c/mL)	Ag/Ab	Ab	Qual	(c/mL)
HPTN 083												
[redacted] (b) (6)	1	<0.025	-		-				-		+	4,010
(A1)	15	6.580	-		-				-		+	<40
	29	3.228	-		+	-		50	-		+	78
[redacted] (b) (6)	1	<0.025	-		-				+	-	+	44,180
(A4)	18	5.587	-		-				-		+	<40
	31	4.964	-		-				-		-	
	39	2.636	-		-				-		-	
	46	2.113	-		-				-		+	<40
	64	2.997	-		+				-	-	-	
[redacted] (b) (6)	28	6.301	-		-				-		+	120
(C1)	***37***	1.839	-		-				-		+	161
	45	1.219	-		-				-		+	137
	65	1.841	-		-				-		+	2,174
	75	3.469	-		+			1,139	+	-	+	1,373
[redacted] (b) (6)	133	2.017	-		-				-		+	<40
(D4)	***178***	1.930	-		+		+	174	+	±	+	158
[redacted] (b) (6)	20	10.690	-	-	-				-		+	ND
(C3)	28	8.767	-	-	-				-		+	<40
	35	4.488	-	-	-				-		-	ND
	41	1.582	-	-	-				-		+	99
	55	1.108	+	+	+				+	±	+	102,329
[redacted] (b) (6)	***120***	1.504	-		-				-		+	860
(D3)	169	1.538	-		-				-		+	ND
	182	1.213	-		-				-		+	<40
	196	1.848	-		-				-		+	112
	232	1.220	-		±				+	-	+	7,160
	237	1.645	+		±			4,628	+	±	+	5,510
[redacted] (b) (6)	1	<0.025	-		-				-		+	1,360
(A3)	15	8.867	-		-				+	-	+	<40
	29	10.180	-		-				-		-	
	36	11.210	-		-				-		-	
	43	8.424	-		-				-		+	ND
	66	1.383	-		-				-		-	
	73	5.428	-		+				-		-	
[redacted] (b) (6)	47	<0.025	-		-				-		+	494
(C2)	232	<0.025	+		+			574,646	+	+	+	229,810

			Site Diagnostics						Central Diagnostics			
			Rapid Tests		Ag/Ab Tests		HIV-1 RNA[4]				HIV-1 RNA[4]	
Subject (Code)[1]	Day[2]	CAB (mcg/mL)[3]	1	2	1	2	Qual	(c/mL)	Ag/Ab	Ab	Qual	(c/mL)
(b) (6)	190	1.405	-		-				-		+	ND
(D2)	***232***	1.175	-		-				-		-	
	245	3.207	-		-				-		+	ND
	288	1.795	-		+				-		-	
(b) (6)	1	<0.025	-		-				-		+	50,080
(A2)	20	11.950	-		-				-		+	20,760
	30	4.274	-		-				-		+	700
	41	3.318	-		-				-		+	204
	61	3.840	-		+				+	+	+	1,660
(b) (6)	***393***	1.613	-		-				-		+	130
(D1)	407	2.251	-		-				-		+	163
	449	1.696	-		-				-		+	87
	470	2.514	-		-				-		+	71
	505	1.444	-		+				+	+	+	<40
HPTN 084												
(b) (6)	1	<0.025	-		-				-		+	<40
	15	6.958	-		-				-		+	500
	26	0.147	-		-				-		+	1,740
	33	<0.025	-		-				-		+	6,300
	38	0.557	-		-				+	±	+	87
	60	0.841	-		-				-		-	
	81	2.336	-		-				-		-	
	114	1.934	-		-				-		-	
	148	3.853	-		-				-		-	
	173	1.754	-		-				-		-	
	227	2.581	-		+			ND	+	±	-	

Source: Supplemental Virology Report (201738 / HPTN 083); Supplemental Virology Report (201739 / HPTN 084); ex.xpt, is.xpt, mb.xpt, pc.xpt, (HPTN 083 supplemental); ex.xpt, is.xpt, mb.xpt, pc.xpt (HPTN 084); Software: JMP 15; Excel 365

[1] Applicant-assigned code for subjects, as reported in Marzinke et al. (2021), are shown in parenthesis

[2] Days with CAB injections indicated by bold, italicized text

[3] Plasma CAB concentration. Lower limit of quantification =0.025 mcg/mL.

[4] HIV-1 RNA as detected by a quantitative RT-PCR assay (HIV-1 RNA c/mL). <40 c/mL = HIV-1 RNA detected but below the assay's lower limit of quantification; ND = HIV-1 RNA not detected.

Abbreviations: +, detected; -, not detected; ±, indeterminant; Ab, antibody; Ag, antigen; c/mL, copies/mL; CAB, cabotegravir; HIV-1, human immunodeficiency virus type 1; ND, HIV-1 RNA not detected; Qual, qualitative

Prolonged exposure of CAB monotherapy to HIV-1-infected individuals is expected to increase the risk for selecting viruses resistant to INSTIs. This risk is especially concerning because INSTIs are a component of all currently recommended starting ART regimens for ARV-naïve individuals. As such, minimizing the duration of CAB monotherapy for individuals who are, or who become, infected when using CAB for PrEP is critical for limiting resistance to the important INSTI class.

The local sites relied primarily on rapid tests and a laboratory-based HIV-1 Ag/Ab assay. In most cases where there was a difference between the time of diagnosis between the local site and central laboratory, the infections were successfully identified retrospectively by the central laboratory, which used more sensitive HIV-1 RNA-specific assays in addition to Ag/Ab and Ab-specific tests. Indeed, viral RNA was the sole analyte detected in 92% (11/12) of the initial diagnoses of infected subjects assigned to receive CAB LA and who experienced a delay of diagnosis by the local site; that is, even the central laboratory's Ag/Ab assay did not detect infection at these earliest HIV-1 infection visits. Similarly, 88% (7/8) of the prevalent infections

detected in both HPTN 083 and HPTN 084 were only detected by RNA-specific assays, with both the RNA- and the Ag/Ab-specific assays detecting infection in only 1 of these cases.

The ability of the HIV-1 RNA assays to detect infection was not consistent over time, with 42% (5/12) of cases demonstrating at least one intermittent period of lost sensitivity after showing positive results earlier during infection. These periods of assay negativity are likely due to viral suppression by CAB monotherapy. Interestingly, there was at least a single time point for 80% (4/5) of these subjects where the Ag/Ab assay, conducted by either the local site or central laboratory, was able to diagnose infection successfully while the RNA-specific assay did not.

Collectively, these data indicate that frequent testing (prior to initiating APRETUDE or oral CAB and with each subsequent injection of APRETUDE) using RNA-specific assays should be employed to minimize the time to the diagnosis of HIV-1 infection. Although laboratory-based Ag/Ab assays were able to diagnose infections at some intermediate time points missed by RNA-specific assays when viral replication was suppressed by CAB monotherapy, the RNA-specific assays consistently provided the earliest HIV-1 diagnoses for both prevalent and incident infections.

CAB Resistance

The results of the HIV-1 genotyping analysis for viruses isolated from subjects assigned to use CAB are summarized in Table 58. Viruses harboring at least one major INSTI RAS were detected in 29% (5/17) of the subjects, including variants with L74I+Q148R+E157Q, L74I+E138E/K+G140G/S+Q148R+E157Q, E138K+Q148K, E138A+Q148R, G140A+Q148R, and R263K. The emergence of variants expressing INSTI RAS, or of variants that acquired additional INSTI RAS, was observed in Subjects (b) (6) (C1), (b) (6) (D3), and (b) (6) (A2). As expected, the detection of viruses expressing INSTI RAS was associated with replication, often for extended periods of time, in the presence of CAB concentrations expected to exert antiviral activity. Indeed, all five of the subjects who harbored virus expressing INSTI RAS were among those who experienced delays in the time to diagnosis of infection.

Table 58. CAB Genotypic Resistance, Trials HPTN 083 and HPTN 084

Subject (Code)[1]	Day[2]	CAB[3] (mcg/mL)	HIV-1 RNA (copies/mL)	ST[4]	INSTI RAS[5]
HPTN 083					
(b) (6) A1)	1	<0.025	4,010	B	WT
A4)	1	<0.025	44,180	B	WT
C1)	***65***	1.841	2,174	B	L74I, Q148R, E157Q
	75	3.469	1,373	B	L74I, E138E/K, G140G/S, Q148R, E157Q
	79	3.647	2,549	B	L74I, E138E/K, G140G/S, Q148R, E157Q
D4)	274	2.261	152,730	C	G140A, Q148R
C3)	55	1.108	102,329	B	E138A, Q148R
	56	1.182	218,776	B	E138A, Q148R
D3)	***120***	1.504	860	BF	WT
	232	1.220	7,160	BF	R263K
	237	1.645	5,510	BF	R263K
A3)	1	<0.025	1,360	B	WT
	186	0.586	1,440	B	WT
	249	0.056	76,090	B	WT
C2)	232	<0.025	229,810	BF	WT
	233	2.559	207,810	BF	WT

Subject (Code)[1]	Day[2]	CAB[3] (mcg/mL)	HIV-1 RNA (copies/mL)	ST[4]	INSTI RAS[5]
(b) (6) (A2)	1	<0.025	50,080	C	WT
	20	11.950	20,760	C	WT
	30	4.274	700	C	WT
	61	3.840	1,660	C	E138K, Q148K
	70	2.533	4,829	C	E138K, Q148K
(B5)	350	<0.025	2,559	B	WT
(B1)	957	0.065	65,530	B	WT
(B2)	725	<0.025	53,220	A/B	WT
(B3)	393	0.100	50,440	AE	WT
HPTN 084					
(b) (6)	402	<0.025	42,810	C	WT
	535	<0.025	44,870	C	WT
	77	<0.025	26,840	C	WT
	522	0.416	875,200	C	WT
	526	1.217	3,927,990	C	WT
	15	6.958	500	A1	WT
	26	0.147	1,740	A1	WT
	33	<0.025	6,300	A1	WT

Source: Supplemental Virology Report (201738 / HPTN 083); Supplemental Virology Report (201739 / HPTN 084); ex.xpt, mb.xpt, pc.xpt, pf.xpt (HPTN 083 supplemental); ex.xpt, mb.xpt, pc.xpt (HPTN 084), pf.xpt (HPTN 084 supplemental); Software: JMP 15; Excel 365
[1] Applicant-assigned code for subjects, as reported in Marzinke et al. (2021), are shown in parenthesis
[2] Days with CAB injections indicated by bold, italicized text
[3] Plasma CAB concentration. Lower limit of quantification =0.025 mcg/mL.
[4] HIV-1 subtype
[5] INSTI resistance-associated substitutions
Abbreviations: CAB, cabotegravir; HIV-1, human immunodeficiency virus type 1; INSTI, integrase strand-transfer inhibitor; RAS, resistance-associated substitution; ST, subtype; WT, wild-type (i.e., absence of major INSTI resistance-associated substitutions)

The results of the phenotypic analysis are presented in Table 59. The expression of G140A+Q148R conferred a 13-fold reduction in susceptibility to the CAB, <3-fold reductions in susceptibility to BIC and DTG, and larger reductions in susceptibility to EVG and RAL (107-fold and 43-fold, respectively). The expression of E138A+Q148R conferred an ~6-fold reduction in susceptibility to CAB, small reductions in susceptibility to BIC and DTG (1.2-fold and 1.7-fold, respectively), and larger reductions in susceptibility to EVG and RAL (>130- and 17-fold, respectively). The expression of R263K conferred <5-fold reductions in susceptibility against all the tested INSTIs. The viruses from Subjects (b) (6) (D4) and (b) (6) (C3) are likely to demonstrate at least partial resistance to CAB, EVG, and RAL, while retaining susceptibility to BIC and DTG. However, these INSTI RAS may affect the durability of future BIC and DTG-containing regimens. The virus from (b) (6) (D3) is likely to remain susceptible to all the tested INSTIs, although the presence of R263K might reduce the durability of INSTIs.

Table 59. CAB Phenotypic Resistance, Trial HPTN 083

Trial/Subject (Code)[1]	INSTI RAS	Fold-Change Reduction in EC_{50} Value[2] CAB	BIC	DTG	EVG	RAL
HPTN 084						
(b) (6) (D4)	G140A, Q148R	13	2.77	2.09	107	43
(C3)	E138A, Q148R	5.92	1.2	1.69	>130	17
(D3)	R263K	2.32	2.89	2.29	4.14	1.38

Source: Supplemental Virology Report (201738 / HPTN 083); Software: JMP 15; Excel 365
[1] Applicant-assigned code for subjects, as reported in Marzinke et al. (2021), are shown in parenthesis
[2] Fold-change reductions in susceptibility to indicated INSTI
Abbreviations: BIC, bictegravir; CAB, cabotegravir; DTG, dolutegravir; EC_{50}, half-maximal effective concentration; EVG, elvitegravir; HIV-1, human immunodeficiency virus type 1; INSTI, integrase strand-transfer inhibitor; RAL, raltegravir; RAS, resistance-associated substitution

Conclusions

The benefit-risk assessment for CAB LA for HIV-1 PrEP is highly favorable despite concerns that justify additional risk-mitigation strategies relative to currently approved PrEP products. Although the identification of pharmacologic failures among participants using CAB LA for PrEP is concerning, the overall rate of HIV-1 infections was very low, even when compared to TDF/FTC, an approved PrEP product that is known to be highly efficacious when used as recommended.

Viruses with reduced susceptibility to INSTIs were detected among several participants who were infected prior to beginning CAB LA for PrEP, or who became infected while using CAB LA for PrEP. CAB monotherapy is not expected to fully suppress viral replication efficiently, and several participants experienced periods of viremia despite high concentrations of CAB. In addition to increasing the likelihood that they would acquire INSTI-resistant viruses during these periods and jeopardize future INSTI treatment options, these individuals were at risk of transmitting HIV-1—and perhaps INSTI-resistant variants—to sexual partners, although the risk was likely lower than if they supported a higher level of viremia without the suppressive effects of CAB. Importantly, the suppressed viral replication also delays the time to diagnosis by many HIV-1 diagnostic assays. In our assessment, this delayed diagnosis by standard diagnostic assays necessitates the recommendation of more stringent testing algorithms than what has been recommended for currently approved PrEP products.

The data indicate that frequent testing for HIV-1 infection among people using CAB for PrEP using RNA-specific assays should be employed.

The risk of pharmacologic failure and the development of resistance will be mitigated through labeling and through the collection of additional data on pharmacologic failures and resistance in a 5-year observation postapproval study to be conducted as a postmarketing requirement. Relevant labeling components to this risk mitigation strategy include the following:

- A BOX WARNING stating that negative HIV-1 status must be confirmed prior to initiating APETUDE or VOCABRIA and prior to each APRETUDE injection and describing the risk of drug resistance if APRETUDE is used in the setting of undetected HIV-1 infection
  - Individuals must be tested for HIV-1 infection prior to initiating APRETUDE or oral cabotegravir, and with each subsequent injection of APRETUDE, using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection (b) (4)
- A CONTRAINDICATION in persons with unknown or positive HIV-status
- A WARNING and PRECAUTION on the comprehensive management to reduce the risk of HIV-1 infection
  - This warning indicates that CAB LA is not always effective in preventing HIV-1, that time to onset of protection is unknown, and that CAB LA should be used as part of an overall prevention strategy

7.7.2. Optional Oral Lead-In

Issue

In HPTN 083 and HPTN 084, a 4-week OLI was required to ensure tolerability of CAB prior to initiating the CAB LA injections. No data are currently available to support the safety and efficacy of CAB LA without an OLI for PrEP. The Applicant has proposed an optional OLI based on available efficacy and safety data from FLAIR extension trial conducted in HIV-1 infected patients.

Background

In the HIV-1 treatment and PrEP pivotal trials, a 4-week OLI was used to assess the tolerability of CAB prior to initiating CAB LA. The decision to include an OLI in these trials was based exclusively on a desire to proceed conservatively with regards to safety. At the time that the CAB LA HIV-1 treatment and PrEP trials were being designed, the need for an OLI to achieve therapeutic concentrations of CAB was being discussed. CABENUVA labeling currently requires an OLI. However, efficacy supplements containing revised labeling making the OLI optional for the CABENUVA and VOCABRIA NDAs (212888 and 212887) are currently under review (PDUFA date: March 27, 2022).

The Applicant's proposal to make the OLI optional for HIV-1 treatment is supported by data from the FLAIR extension trial, in which upon completion of the maintenance phase, participants who had been randomized to current antiretroviral regimen were given the option to switch to CAB LA plus RPV LA in the extension phase or be withdrawn from the trial. Those participants who chose to transition to CAB LA plus RPV LA were given the option to complete the extension phase with or without an OLI (decision made by participant with input from the investigator).

There are no data currently available to support the safety and efficacy of CAB LA without an OLI for HIV-1 PrEP. Of note, extension phases are planned for HPTN 083 and HPTN 084, in which participants will be given the option to switch to CAB LA with or without an OLI. However, data from these extension phase trials are not available.

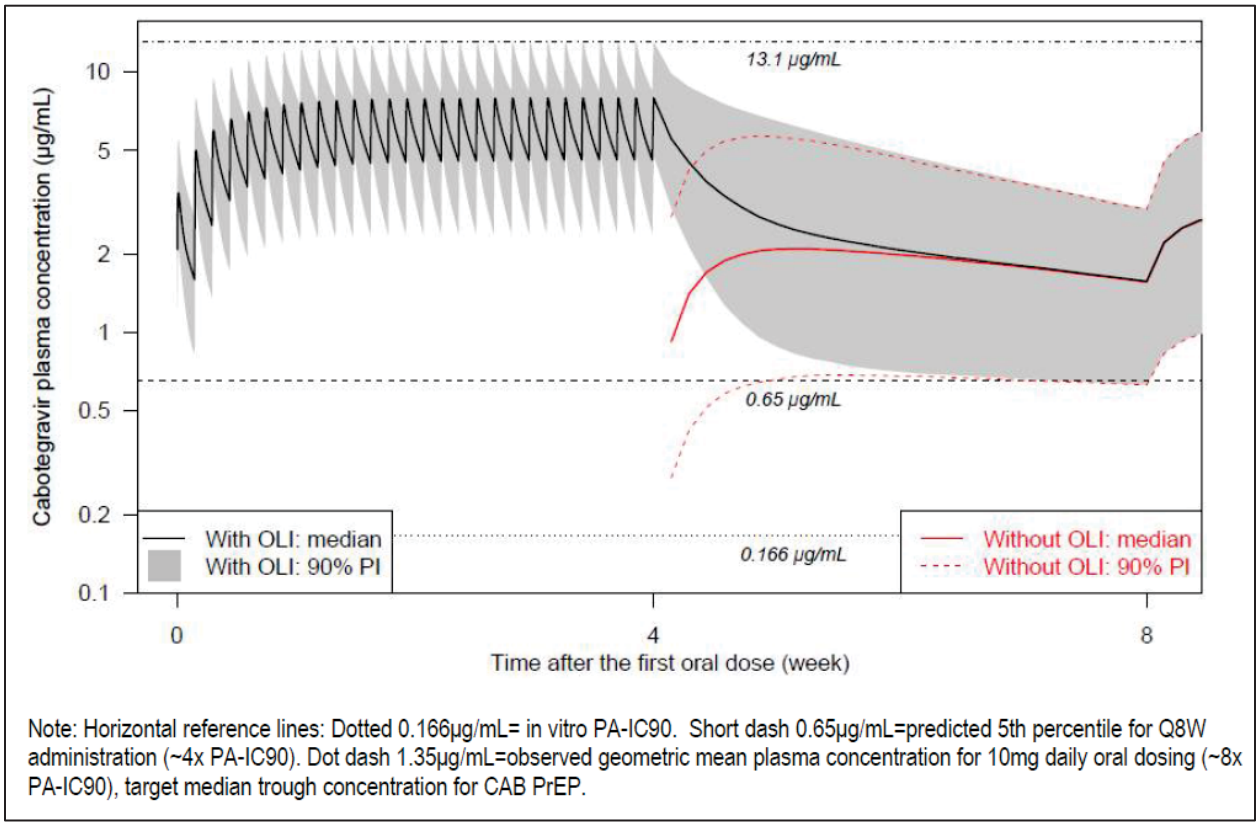
Assessment

In the FLAIR HIV-1 treatment trial, a total of 232 participants entered the extension phase, of whom 111 subjects opted to proceed direct to injection (DTI) and 121 subjects opted for an OLI. During the OLI, 30/121 (25%) participants experienced an AE. None of the AEs reported during the OLI were serious or led to discontinuation. Among the 232 DTI and OLI participants, the overall rate of any AEs over the duration of the extension phase was higher among DTI participants (92/111 (92%) than OLI participants (100/121 (83%). Similarly, the rate of drug-related AEs (86/111 (77%) and 79/121 (65%) of DTI and OLI participants, respectively) and ISRs (87/111 (78%) and 76/121 (64%) of DTI and OLI participants, respectively) were higher among DTI participants than among OLI participants. The rate of SAEs and AEs leading to treatment discontinuation over the course of the extension phase was similar across the two groups (SAEs were reported in 4/111 (4%) and 5/121 (4%) of DTI and OLI participants

respectively; AEs leading to discontinuation were reported in 1/111 (<1%) and 2/121 (2%) of DTI and OLI participants, respectively). Regarding efficacy, the proportion of subjects with HIV-1 RNA ≥50 c/mL was similar across groups (0.8% and 0.9% in the OLI and DTI groups, respectively. These data suggest that CAB LA plus RPV LA is generally safe, well-tolerated, and effective for HIV-1 treatment with or without an OLI.

Simulations conducted to compare CAB concentrations after the first injection following a 4-week OLI versus following the first injection without a 4-week OLI showed that trough concentrations at 4 weeks following the first injection (at Week 8) are nearly identical for both groups. In the OLI group, 95th percentile CAB concentrations are above the target concentration of 0.65 mcg/mL by day one after the initial oral dose, while in the DTI group, 95th percentile CAB concentrations are above the target concentration at one week following the initial injection (Figure 8).

Figure 8. Contribution of OLI to Plasma CAB Concentrations Following the Initial CAB LA Injection Limited to ~1 Week



Note: Horizontal reference lines: Dotted 0.166µg/mL= in vitro PA-IC90. Short dash 0.65µg/mL=predicted 5th percentile for Q8W administration (~4x PA-IC90). Dot dash 1.35µg/mL=observed geometric mean plasma concentration for 10mg daily oral dosing (~8x PA-IC90), target median trough concentration for CAB PrEP.

Source: NDA 215499, SDN 9.

In HPTN 083 and HPTN 084, all participants received OLI prior to initiating injections. In both trials, the rate of AEs, SAEs, and AEs leading to treatment discontinuation during the OLI was comparable in the CAB and TDF/FTC groups. Notably, there were three participants in the CAB group of HPTN 083 who discontinued treatment during the OLI due to rash AEs, two of which were assessed to be drug-related. None of the rash AEs leading to treatment discontinuation were serious or associated with systemic symptoms.

Table 60. Rash Adverse Events Leading to Treatment Discontinuation During the OLI in Participants in the CAB Group, Trial HPTN 083

Subject ID	Preferred Term	Start Day	Duration of AE (Days)	Grade	Serious (Y/N)	Drug-Related (Y/N)
(b) (6)	Pruritic rash	4	24	3	N	Y
	Rash	1	11	1	N	Y
	Eczema	6	123	1	N	N

Source: ADAE dataset, Analysis conducted in JMP version 15

There were three participants who experienced HIV-1 seroconversion during the OLI in HPTN 083. One of these participants (C2) had nonquantifiable plasma CAB concentrations at Weeks 2 and 4 and was HIV-1 positive at the Week 4 visit. Therefore, this seroconversion is thought to be due to nonadherence and is not considered a pharmacologic failure. The other two participants who seroconverted during the OLI (C1 and C3) had plasma CAB concentrations >0.65 mcg/mL (>4x PA-IC_{90}) at Weeks 2, 4, 5, and 9. However, it remains possible that there were subtherapeutic plasma CAB concentrations at other time points in between PK sampling.

Although a DTI approach has not yet been studied in a HIV-1 PrEP setting, the available data from HIV-1 treatment and PrEP trials suggest that an OLI is not needed to assess safety prior to initiating CAB LA. Furthermore, results of simulations (Figure 8) indicating that the contribution of OLI to the plasma CAB concentrations is limited to the first week following the initial injection and the similarity in efficacy between HIV-1 infected patients who received the OLI versus those who did not in the FLAIR extension trials suggest that an OLI is not needed to achieve target plasma CAB concentrations. Lastly, poor adherence to OLI may be associated with unpredictable plasma CAB concentrations and increased risk of HIV-1 seroconversion; hence CAB LA without an OLI may be an appropriate alternative.

Section 2 of the APRETUDE package insert presents both an OLI approach and a DTI approach as acceptable options for CAB LA administration. Findings from the CABENUVA experience are summarized in Section 2 to support the DTI approach. Additional data regarding the safety, acceptability, and effectiveness of the DTI approach for HIV-1 PrEP will become available in the coming years as the HPTN extension studies and the CAB LA for HIV-1 PrEP observational study are completed. APRETUDE labeling will be updated with these data as appropriate.

Conclusion

The FLAIR extension trial suggests that in an HIV-1 treatment setting, CAB LA+RPV LA is safe and effective with or without an OLI. There are no data available regarding the use of CAB LA in a prevention setting without an OLI. However, it would be reasonable to expect the safety of CAB LA to be similar in HIV-1-infected and uninfected populations. Further, the OLI in HPTN 083 and HPTN 084 did not identify any concerning safety findings that precluded participants from going on to the injection phase of the study. Lastly, regarding efficacy, an OLI is not needed to achieve “adequate” plasma CAB concentrations (based on the assumption that CAB trough concentration determined to be adequate when CAB/RPV LA is administered to HIV-1 infected patients will also be adequate to prevent HIV-1 acquisition with CAB LA monotherapy) and the efficacy data from the FLAIR extension trial.

While there are no data available to confirm that a direct to injection approach is as safe and effective as an OLI approach for HIV-1 PrEP (as evaluated in trials HPTN083 and HPTN084), the HPTN trials did show that HIV-1 seroconversions can occur during the OLI. The effectiveness of CAB during the OLI is dependent on high daily medication adherence. Given

that participants who do not want to take a daily pill are more likely to choose CAB LA for HIV-1 PrEP over the other approved oral PrEP options, adherence during the OLI may be challenging for some participants. In these patients, the OLI may be a period of increased risk for HIV-1 acquisition.

Based on the available data, the review team concludes that in some persons an OLI may be beneficial while in others it may be detrimental. The decision to start with an OLI or to go directly to injections should be left to the discretion of the patient and the healthcare provider.

8. Therapeutic Individualization

8.1. Intrinsic Factors

See the original NDA review (NDA 212888, integrated review dated December 19, 2019).

8.2. Drug Interactions

See the original NDA review (NDA 212888, integrated review dated December 19, 2019).

8.3. Plans for Pediatric Drug Development

As outlined in the Agreed Initial Pediatric Study Plan, CAB LA for HIV-1 PrEP was granted a full waiver in neonates, infants, and children from birth to less than 12 years of age. Additionally, a deferral for adolescents from 12 to 17 years of age was issued. However, the Applicant is seeking an indication in adolescents in the initial APRETUDE application. The available data to support an indication in adolescents are summarized below.

Clinical Data

The Applicant has initiated two HIV-1 PrEP sub-studies in adolescents: HPTN 083-01 and HPTN 084-01. These are both single-arm, open-label, safety, tolerability, and acceptability studies in sexually active, HIV-1-uninfected adolescent males (HPTN 083-01) and females (HPTN-084-01). Participants first receive a 5-week CAB OLI followed by five CAB injections administered at 8-week intervals after a 4-week loading dose. At the time of the last DSMB review (data cut-off of September 1, 2021), HPTN 083-01 had enrolled four male participants, all of whom had received 1 or more CAB injections. In HPTN 084-01, 55 female participants have been enrolled. Of these, 50 participants have received one or more CAB injections. Across both sub-studies, there has been one treatment discontinuation, and this occurred before the participant had received any CAB. There have been no Grade 4 AEs. One out of four (25%) participants in HPTN 083-01 reported an ISR; in HPTN 084-01, 12 of the 50 (24%) participants who received 1 or more injection reported 1 or more ISRs. All ISRs were Grade 1 or 2 in severity. There have been no pregnancies and no HIV seroconversions.

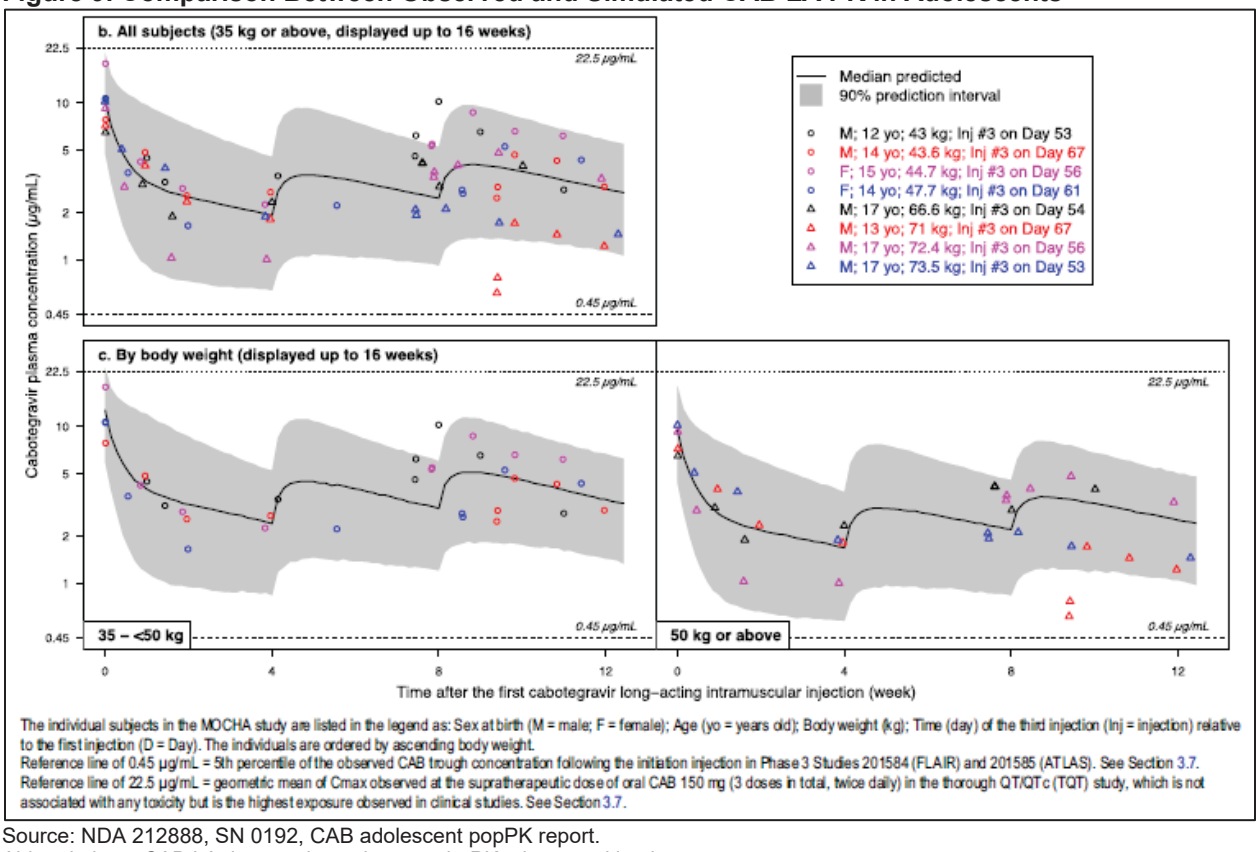
The Applicant also has an ongoing HIV-1 treatment trial in adolescents, the More Options for Children and Adolescents (MOCHA) trial. At the time of this review, some safety and PK data from Cohort 1 of MOCHA were available. In Cohort 1, HIV-infected adolescents were assigned to receive either 4 weeks of oral CAB followed by CAB LA Q4W or 4 weeks of oral RPV followed by RPV LA Q4W on top of their background combination ART regimen. Among eight

participants who were assigned to the CAB arm and had received both oral and injectable CAB, no new safety concerns were identified. There were no SAEs and no discontinuations due to AEs. Five (62.5%) of participants had experienced an ISR. Three (37.5%) had reported ≥Grade 3 AEs, one of which was drug-related (PT = insomnia).

Pharmacokinetic Data

Predicted exposures for adolescents (age 12 to <18 years and ≥35 kg) administered CAB IM Q4W and obtained prior to enrollment of adolescents in MOCHA were consistent with observed adolescent PK data in MOCHA (n=8, weight range 43-74 kg), supporting use of the model to predict exposures in adolescents ≥35 kg administered CAB IM Q8W (Figure 9).

Figure 9. Comparison Between Observed and Simulated CAB LA PK in Adolescents



Source: NDA 212888, SN 0192, CAB adolescent popPK report.
Abbreviations: CAB LA, long-acting cabotegravir; PK, pharmacokinetics

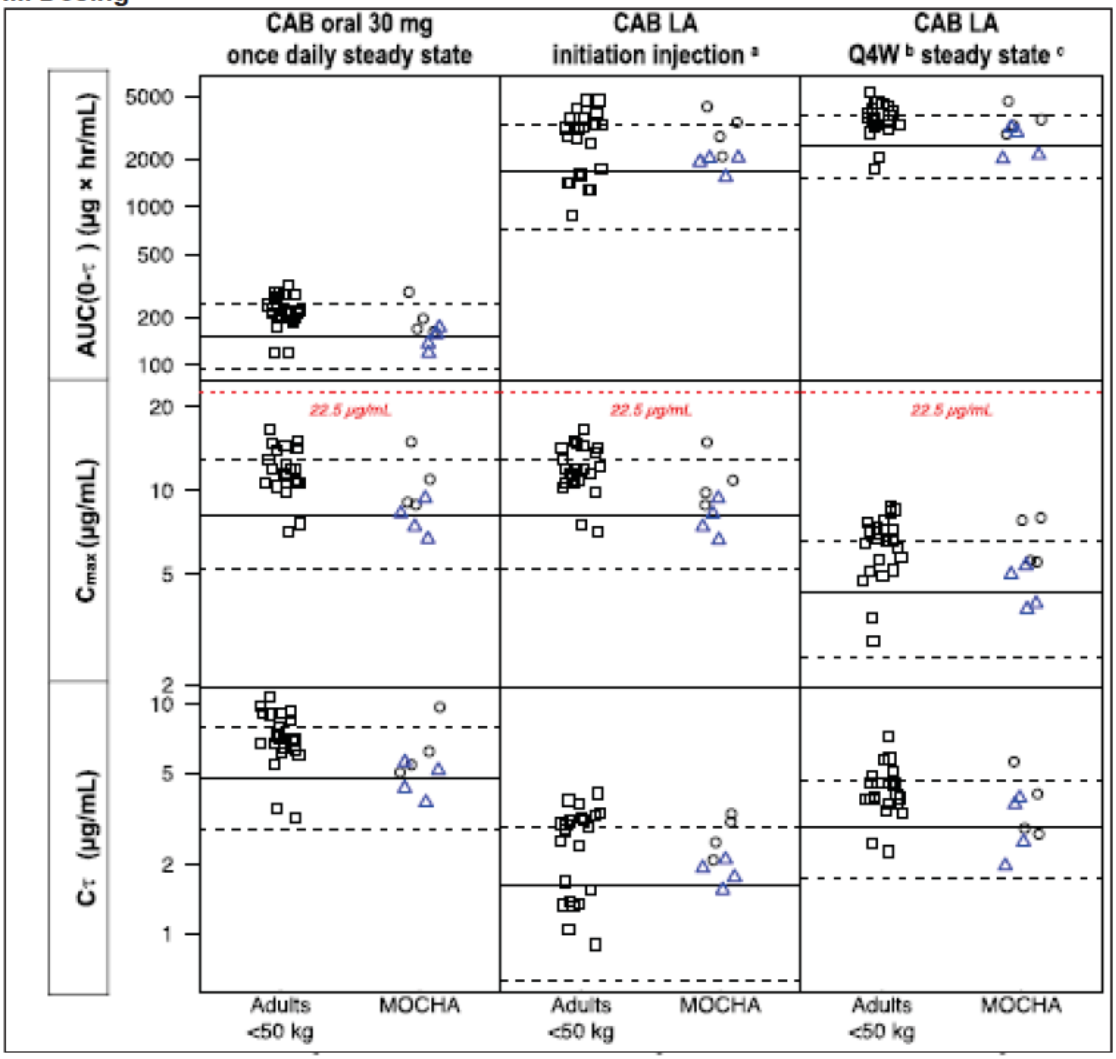
In adolescents administered CAB IM Q4W with available PK data (n=8), CAB exposures were generally within the 5th to 95th percentile range of adults and had a similar distribution when compared to adults <50 kg across the development program (Figure 10). Four of eight MOCHA adolescents had body weight <50 kg.

Observed exposures in adolescents and adults administered CAB IM Q4W and adults administered CAB IM Q8W were incorporated into the CAB population pharmacokinetic model and exposures were predicted for adolescents administered CAB IM Q8W (see Section 14.1).

While the distribution of CAB maximum plasma concentration following OLI and Q8W IM dosing is higher in adolescents versus adults, ~5% of adolescents during OLI and the initial injection are expected to have plasma CAB concentrations >22.5 mcg/mL (22.5 mcg/mL was the

mean maximum plasma concentration at a supratherapeutic dose of 150 mg in the QT study, which was not associated with toxicity, see Table 61 and Table 62). CAB exposures are highest during OLI. Among eight subjects enrolled in MOCHA, median (range) maximum plasma concentration (C_{max}) values during OLI were 9.0 mcg/mL (6.7-15.0). The majority of the duration of CAB IM therapy will consist of maintenance Q8W injections, where C_{max} values are lower than during the OLI and initial injection (predicted 95th percentile of CAB C_{max} during maintenance injections is 14.1 mcg/mL) (Table 62).

Figure 10. CAB exposures in Adolescents Vs. Adults Weighing <50 kg After Oral Lead-In and Q4W IM Dosing



CAB = cabotegravir; IM = intramuscular; LA = long-acting; PO = oral; QD = daily; SS = steady state.
Solid (dashed) lines = median (5th and 95th percentiles) of exposure in 1387 adults from Phase 3 studies 201584, 201585 and 207966; Black square = 23 adults with body weight of <50 kg (15 were from Phase 3 studies 201584, 201585 and 207966, and therefore included in calculation of median, 5th and 95th percentiles of adult exposure); Black circle = 4 adolescents in the MOCHA study with body weight of <50 kg; Blue triangle = 4 adolescents in the MOCHA study with body weight of ≥50 kg.

Continued

Figure 10, continued

Reference line of 22.5 µg/mL = geometric mean of Cmax observed at the supratherapeutic dose of oral CAB 150 mg (3 doses in total, twice daily) in the thorough QT/QTc (TQT) study, which is not associated with any toxicity but is the highest exposure observed in clinical studies.

a. C_{max} following CAB LA initiation injection is predominantly determined by the last oral dose instead of the LA injection.
b. Q4W CAB LA dosing regimen: CAB PO dose of 30 mg QD for 4 weeks, and then 600 mg CAB LA IM (initiation injection) at 2 hours after the last CAB PO dose, followed by 400 mg CAB LA IM (maintenance dose) Q4W starting at 4 weeks after the initiation injection.
c. Q4W steady state: 11th CAB LA IM Injection (40-44 weeks after initiation injection)

Source: NDA 212888, SN 0192, CAB adolescent popPK report.

Table 61. Pharmacokinetic Parameters in Adults Following Once-Daily Oral Cabotegravir and Followin Initiation and Ever -2-Month Continuation Intramuscular Injections of CAB

Dosing Phase	Dosage Regimen	Geometric Mean (5th, 95th Percentile)[a]		
		$AUC_{(0\text{-}tau)}$[b] (mcg•h/mL)	C_{max} (mcg/mL)	C_{tau} (mcg/mL)
Oral lead-in[c]	30 mg once daily	145 (93.5, 224)	8.0 (5.3, 11.9)	4.6 (2.8, 7.5)
Initial injection[d]	600 mg IM initial dose	1,591 (714; 3,245)	8.0 (5.3, 11.9)	1.5 (0.65, 2.9)
Every-2-month injection[e]	600 mg IM every 2 months	3,764 (2,431; 5,857)	4.0 (2.3, 6.8)	1.6 (0.8, 3.0)

IM = Intramuscular.

[a] Pharmacokinetic parameter values were based on individual post-hoc estimates from cabotegravir population pharmacokinetic models for patients in Phase 3 treatment studies of HIV treatment.

[b] tau is dosing interval: 24 hours for oral administration, 1 month for the initial injection, and 2 months for every 2 months for intramuscular injections of extended-release injectable suspension.

[c] Oral lead-in pharmacokinetic parameter values represent steady state.

[d] Initial injection C_{max} values primarily reflect oral dosing because the initial injection was administered on the same day as the last oral dose; however, $AUC_{(0\text{-}tau)}$ and the C_{tau} values reflect the initial injection. When administered without oral lead-in to HIV-infected recipients (n = 110), the observed cabotegravir geometric mean (5th, 95th percentile) C_{max} (1-week post-initial injection) was 1.89 mcg/mL (0.438, 5.69) and C_{tau} was 1.43 mcg/mL (0.403, 3.90).

[e] Pharmacokinetic parameter values represent steady state.

Source: NDA 215499, SDN 28.

Table 62. Pharmacokinetic Parameters in Adolescents ≥35 kg Following Once-Daily Oral Cabotegravir and Following Initiation and Every-2-Month Continuation Intramuscular Injections of CAB

Dosing Phase	Dosage Regimen	Geometric Mean (5th, 95th Percentile)[a]		
		$AUC_{(0\text{-}tau)}$[b] (mcg•h/mL)	C_{max} (mcg/mL)	C_{tau} (mcg/mL)
Oral lead-in[c]	30 mg once daily	193 (106, 346)	14.4 (8.02, 25.5)	5.79 (2.48, 12.6)
Initial injection[d]	600 mg IM initial dose	2,123 (881; 4,938)	11.2 (5.63, 21.5)	1.84 (0.64, 4.52)
Every-2-month injection[e]	600 mg IM every 2 months	4,871 (2,827; 8,232)	7.23 (3.76, 14.1)	2.01 (0.64, 4.73)

IM = intramuscular.

[a] Pharmacokinetic (PK) parameter values were based on population PK model simulations in a virtual HIV-1 infected adolescent population weighing 35 to 156 kg.

[b] tau is dosing interval: 24 hours for oral administration, 1 month for the initial injection, and 2 months for every 2 months for IM injections of extended-release injectable suspension.

[c] Oral lead-in pharmacokinetic parameter values represent steady state.

[d] Initial injection C_{max} values primarily reflect oral dosing because the initial injection was administered on the same day as the last oral dose; however, the $AUC_{(0\text{-}tau)}$ and C_{tau} values reflect the initial injection.

[e] PK parameter values represent steady state.

Source: NDA 215499, SDN 28

Conclusions

The review team finds that the safety and efficacy of APRETUDE for HIV-1 PrEP in HIV-1 uninfected adolescents is supported by the safety and PK of CAB LA in HIV-1-uninfected adults in HPTN 083 and HPTN 084 as well as in HIV-1-infected adolescents in MOCHA. Though only limited data are available from HIV-1-uninfected adolescents in HPTN 083-01 and HPTN 084-01, no new safety concerns have been identified in these trials to date.

The basis for approving APRETUDE for use in adolescents will be described in Section 8 of the APRETUDE label.

8.4. Pregnancy and Lactation

Clinical Data

In HPTN 084 there were 38 participants in the CAB arm reporting 40 pregnancies and 34 participants in the TDF/FTC arm reporting 37 pregnancies. Of these pregnancies, 29 and 20 were confirmed pregnancies in the CAB and TDF/FTC arms, respectively. A confirmed pregnancy was defined as when a participant had a pregnancy outcome and/or two positive pregnancy tests, except in the case when a participant had an abortion before a second positive pregnancy test. The outcomes of the 77 reported pregnancies are summarized in Table 63. There were no congenital anomalies reported among pregnancies from either arm. Premature term live births,

spontaneous abortions, stillbirth/intrauterine fetal demises, and ectopic pregnancies were rare and occurred in a similar proportion of CAB and TDF/FTC pregnancies.

There are no pregnancy data from HPTN 083 as this trial enrolled only male participants.

Table 63. Pregnancy Outcomes, Safety Population, Trial HPTN 084

Pregnancy Outcomes	CAB N=1614 n (%)	TDF/FTC N=1610 n (%)
Reported pregnancies	40 (2.5)	37 (2.3)
Pending confirmation	3 (0.2)	5 (0.3)
Ended before confirmatory test	8 (0.5)	12 (0.7)
Confirmed	29 (1.8)	20 (1.2)
Ongoing pregnancies	11 (0.7)	7 (0.4)
Pregnancies with obtainable outcome	27 (1.7)	24 (1.5)
Full term live birth ≥37 weeks)	10 (0.6)	10 (0.6)
Premature term live birth (<37 weeks)	3 (0.2)	0 (0)
Spontaneous abortion (<20 weeks)	5 (0.3)	6 (0.4)
Stillbirth/Intrauterine fetal demise ≥20 weeks	1 (0.1)	1 (0.1)
Therapeutic/Elective abortion	7 (0.4)	6 (0.4)
Ectopic pregnancy	1 (0.1)	1 (0.1)
Congenital anomalies	0 (0)	0 (0)

Source: ADPREG
Abbreviations: CAB, cabotegravir; TDF/FTC, emtricitabine/tenofovir disoproxil fumarate

9. Product Quality

Approval—The Office of Pharmaceutical Quality review team has assessed NDA 215499 with respect to chemistry, manufacturing, and controls, and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. The CAB injectable suspension, 600 mg/3 mL and associated devices are exactly the same product copackaged and registered in NDA 212888, with the same manufacturing sites, processes and specifications. The stability results support the proposed shelf life 36 months at a combined room temperature and refrigerated condition of 2°C to 25°C (36°F to 77°F). The Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective.

9.1. Device or Combination Product Considerations

The Center for Devices and Radiological Health recommends approval for the device constituent. The Applicant used 510(k) cleared devices and a needle with a safety feature in their to-be-marketed kit. The device description, design controls, risk analysis, design verification, clinical validation, labeling, and quality systems/manufacturing controls were acceptable.

There are no outstanding unresolved information requests or any outstanding deficiencies. No postmarketing commitments or postmarketing requirements are recommended.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

A total of five clinical investigator sites were selected for audit. The clinical sites were chosen primarily based on numbers of enrolled subjects, prior inspection history and protocol deviations. The clinical investigators Drs. Kelley, Mayer, and Landovitz (all in the United States) were inspected for Protocol 201738/HPTN 083. For Drs. Mokgoro and Bekker in South Africa, remote regulatory assessments were performed for Protocol 201738/HPTN 084 as an alternative to onsite inspections due to pandemic travel restrictions. No evidence of unreported HIV-1 seroconversions was found at any site. With the exception of two unreported AEs among participants in the TDF/FTC arm of HPTN 083 (from Dr. Landovitz's site), there was no evidence of underreporting of AEs. The results of the clinical sites inspections support the conclusion that the studies were conducted adequately, and the data generated appear to be acceptable in support of this NDA.

Please see Section 23 for the Financial Disclosure summary.

11. Advisory Committee Summary

CAB LA for HIV-1 PrEP was not taken to an FDA advisory committee because no unexpected significant safety or efficacy issues were identified, and no controversial issues arose that would benefit from advisory committee discussion.

III. Appendices

12. Summary of Regulatory History

IND 101429 for GSK1265744, subsequently renamed cabotegravir (CAB), oral formulation, for the treatment of HIV-1 infection was submitted by GlaxoSmithKline LLC on January 21, 2008, and deemed safe to proceed on February 21, 2008. A type C meeting to discuss the development of cabotegravir long-acting (CAB LA) injectable for the treatment of HIV-1 infection was held on September 3, 2010. The Agency provided guidance on the nonclinical studies needed to support subcutaneous and intramuscular dosing and the design of the phase 1 study(ies) in health volunteers.

IND 109678 for CAB LA injection for the treatment of HIV-1 infection was submitted by GlaxoSmithKline on September 17, 2010, and deemed safe to proceed on October 15, 2010.

On October 1, 2011, GlaxoSmithKline transferred sponsorship of IND 101429 to ViiV Healthcare Company.

A request for a type C guidance meeting was submitted to IND 109678 to discuss the development program for CAB tablets and CAB LA injection for HIV-1 pre-exposure prophylaxis (PrEP). The meeting was held was on November 19, 2013, during which the Agency provided guidance on the design of the phase 2 studies HPTN 077 and ÉCLAIR (study 2011120), as well as the CAB tablet one-month oral lead-in (OLI) dosing safety database needed to support the submission of an NDA for HIV-1 PrEP. An indication of HIV-1 PrEP to reduce the risk of HIV-1 infection was added to IND 109678.

On May 8, 2014, the Division of Acquired Immunodeficiency Syndrome (DAIDS), National Institute for Allergy and Infectious Diseases submitted protocol HPTN 077 under IND 122744. In addition to HPTN 077, the future phase 2/3 studies that would investigate the use of CAB and CAB LA for HIV-1 PrEP (studies HPTN 083, HPTN 084, and the studies in adolescents 12 to less than 18 years of age) were conducted under this IND.

On May 29, 2014, IND 109678 for CAB LA injection was granted Fast Track designation for the prevent of acquisition of HIV-1 infection.

Under IND 109678, a type C meeting was held on September 17, 2015, to discuss ViiV's plans to develop CAB tablet as an OLI for CAB LA for the treatment of HIV-1. However, ViiV provided the Agency with the results from the ÉCLAIR study, a phase 2a pharmacokinetic and safety trial in HIV-1-uninfected cisgender men who have sex with men (MSM) that showed an every-12-week dosing regimen resulted in lower than expected exposures. As a result, an every-8-week dosing regimen would be explored in the PrEP trial HPTN 077 that was being conducted under the National Institute for Allergy and Infectious Diseases IND 122744.

An end-of-phase 2 meeting for IND 109678 was held on June 14, 2017, for CAB LA for PrEP. The Agency provided feedback on the design of the vaccine challenge study, phase 3 study HPTN 084, the proposal to make the one-month OLI dosing regimen optional, and the plan to pursue an every-8-week CAB LA injection dosing regimen.

A type C guidance meeting request was submitted under IND 109678 and the meeting was held on September 17, 2020. The purpose of the meeting was to discuss the most efficient pathway for NDA submission of CAB LA for HIV-1 PrEP (b) (6) The Agency provided feedback on the data that would be needed to support the use of the product in cisgender women if trial HPTN 084 is stopped prematurely for administrative reasons or if it continued beyond the November 2020 MDSMB review.

Under IND 109678, CAB LA in combination with safer sex practices was granted Breakthrough Therapy designation on November 16, 2020, for the indication of PrEP to reduce the risk of sexually acquired HIV-1 in individuals at high risk. In HPTN 083, CAB LA was shown to be superior to FTC/TDF for the prevention of HIV-1 in MSM and TGW. Subsequently, in HPTN 084, CAB LA was found to be superior to FTC/TDF for the prevention of HIV-1 in cisgender women. In addition to demonstrating improved efficacy over FTC/TDF (the only approved therapy at the time trials HPTN 083 and HPTN 084 were initiated), CAB LA offered a much-needed alternative approach to HIV-1 PrEP for patients who are not willing or able to take an oral medication daily.

On January 21, 2021, NDA 212887 for VOCABRIA (CAB) 30-mg tablet and NDA 212888 for CABENUVA (CAB; rilpivirine (RPV)) extended-release injectable suspensions were approved. VOCABRIA was approved as an OLI to assess the tolerability of CAB prior to administration of CABENUVA extended-release injectable suspensions and for short-term dosing for patients who plan to miss a scheduled injection. CABENUVA was approved as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral (ARV) regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL (c/mL)) on a stable ARV regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV.

A type B pre-NDA meeting was held on February 19, 2021, to discuss ViiV's proposed strategy for submission and filing of an original NDA for CAB LA for HIV-1 PrEP, including use of VOCABRIA as an OLI. ViiV expressed plans to submit a rolling application in 3 parts, the final piece of the application would be submitted in July 2021. The Agency requested submission of adolescent data from the PrEP substudies and MOCHA trial study (treatment) to support the use of the products in pediatric patients 12 to less than 18 years of age.

On April 16, 2021, the FDA concluded the proprietary name of APRETUDE for CAB LA for PrEP was conditionally acceptable.

Rolling Review designation as granted by the FDA on April 28, 2021. ViiV provided a rolling review delivery timeline with delivery of the NDA application in three parts as follows: Delivery 1 – April 2021, Delivery 2: May 2021, and Delivery 3 – July 2021.

The NDA submission includes a request for a partial waiver in the pediatric patients from birth to less than 12 years of age and a deferral for adolescents from 12 years of age to less than 18 years of age.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

All pivotal nonclinical safety studies were submitted and reviewed under NDAs 212887 and 212888 for the treatment of HIV-1 infection. No additional nonclinical studies or data have been requested or are needed at this time. Overall, the nonclinical safety assessment for CAB was considered acceptable from a pharmacology/toxicology perspective to support approval for the present indication (HIV-1 PrEP).

13.2. Individual Reviews of Studies Submitted to the NDA

Not applicable.

14. Clinical Pharmacology: Additional Information and Assessment

14.1. Pharmacometrics Review

The CAB population pharmacokinetic model was previously reviewed and considered acceptable to support presentation of predicted adult pharmacokinetic (PK) parameters in labeling and to support labeling recommendations for adults with missed injections (NDA 212888, integrated review dated December 19, 2019). The model was updated by fixing allometric exponents to 0.75 for clearances and 1 for volumes of distribution for use of the model to predict exposures in adolescents. These changes lead to minimal changes in model parameters (Table 64).

Table 64. Comparison of Parameter Estimates Between the Final CAB PopPK Model (Final110) and the Revised Model Final111

Parameter	Estimate		IIV (%)		Shrinkage (%)	
Model	final110	final111	final110	final111	final110	final111
KA1 (hr^{-1})	1.41	1.40	89.4	88.7	69.1	69.1
KA2 (hr^{-1})	0.000733	0.000735	57.9	57.9	17.9	17.9
CL/F (L/hr)	0.151	0.151	23.3	23.5	10.3	10.3
V2/F (L)	5.27	5.27	20.3	22.0	31.1	30.7
Q/F (L/hr)	0.507	0.507				
V3/F (L)	2.43	2.42				
F1	0.756	0.758	17.4	17.5	40.0	40.2
Add Err (µg/mL)	0.0319	0.0318				
Prop Err	27.3%	27.3%				
BWT (kg) on CL/F and Q/F	0.618	0.75 fixed				
BWT (kg) on V2/F and V3/F	0.702	1 fixed				
Smoke on CL/F	17.4%	17.6%				
BMI (kg/m^2) on KA2	-0.766	-0.732				
NDL (inch) on KA2	0.478	0.482				
Sex at birth on KA2	-50.9%	-51.4%				
Split on KA2	47.8%	48.1%				

Add Err = additive component of residual variability; BMI = body mass index; BWT =baseline body weight; CI = confidence interval; CL/F = apparent central clearance; F1 = relative bioavailability of the oral relative to IM formulation; IIV = inter-individual variability; IM = intramuscular; KA1 = absorption rate constant for oral tablet; KA2 = absorption rate constant for IM injection; NDL = needle length; PK = pharmacokinetic(s); Prop Err = proportional component of residual variability; Q/F = apparent inter-compartmental clearance; Smoke = current smoker status; Split = split injection; V2/F = apparent central compartment volume of distribution; V3/F = apparent peripheral compartment volume of distribution.

Model final111 equations:

$$\text{KA2} = 0.000735 \times (1 - 51.4\% \text{ if female}) \times (1 + 48.1\% \text{ if split}) \times \left(\frac{BMI}{25.4}\right)^{-0.732} \times \left(\frac{NDL}{1.5}\right)^{0.482}$$

$$\text{CL/F} = 0.151 \times \left(\frac{\text{BWT}}{76.6}\right)^{0.75} \times (1 + 17.6\% \text{ if current smoker})$$

$$\text{V2/F} = 5.27 \times \left(\frac{\text{BWT}}{76.6}\right)^{1}$$

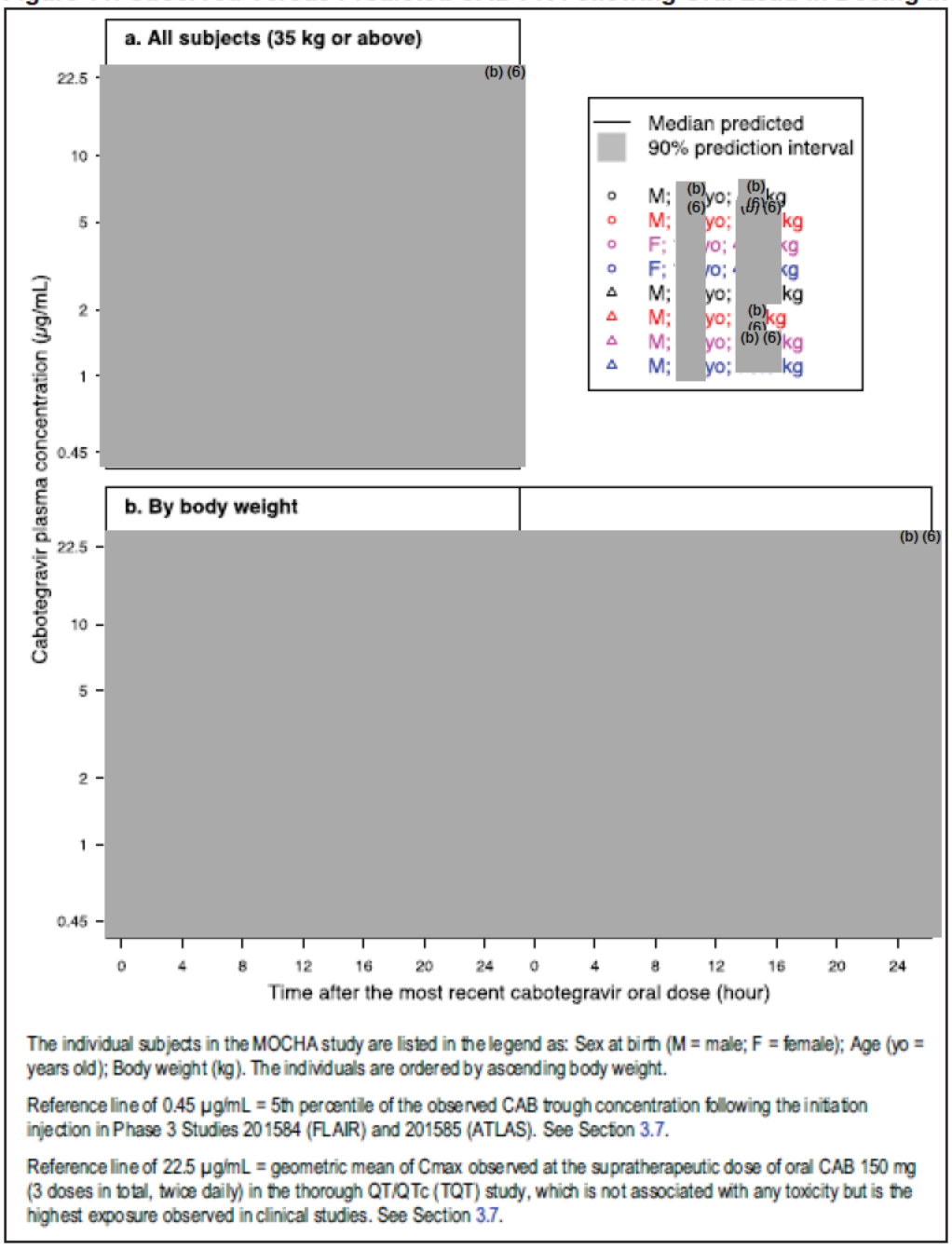
$$\text{Q/F} = 0.507 \times \left(\frac{\text{BWT}}{76.6}\right)^{0.75}$$

$$\text{V3/F} = 2.42 \times \left(\frac{\text{BWT}}{76.6}\right)^{1}$$

Source: NDA 212888, SN 0192.

The model captured observed Q4W OLI and Q4W injection PK data in adolescents (Figure 11, Figure 12) and is acceptable for the purpose of predicting CAB exposures in adolescents following Q8W IM injection dosing (Figure 13, Table 65).

Figure 11. Observed Versus Predicted CAB PK Following Oral Lead-in Dosing in Adolescents



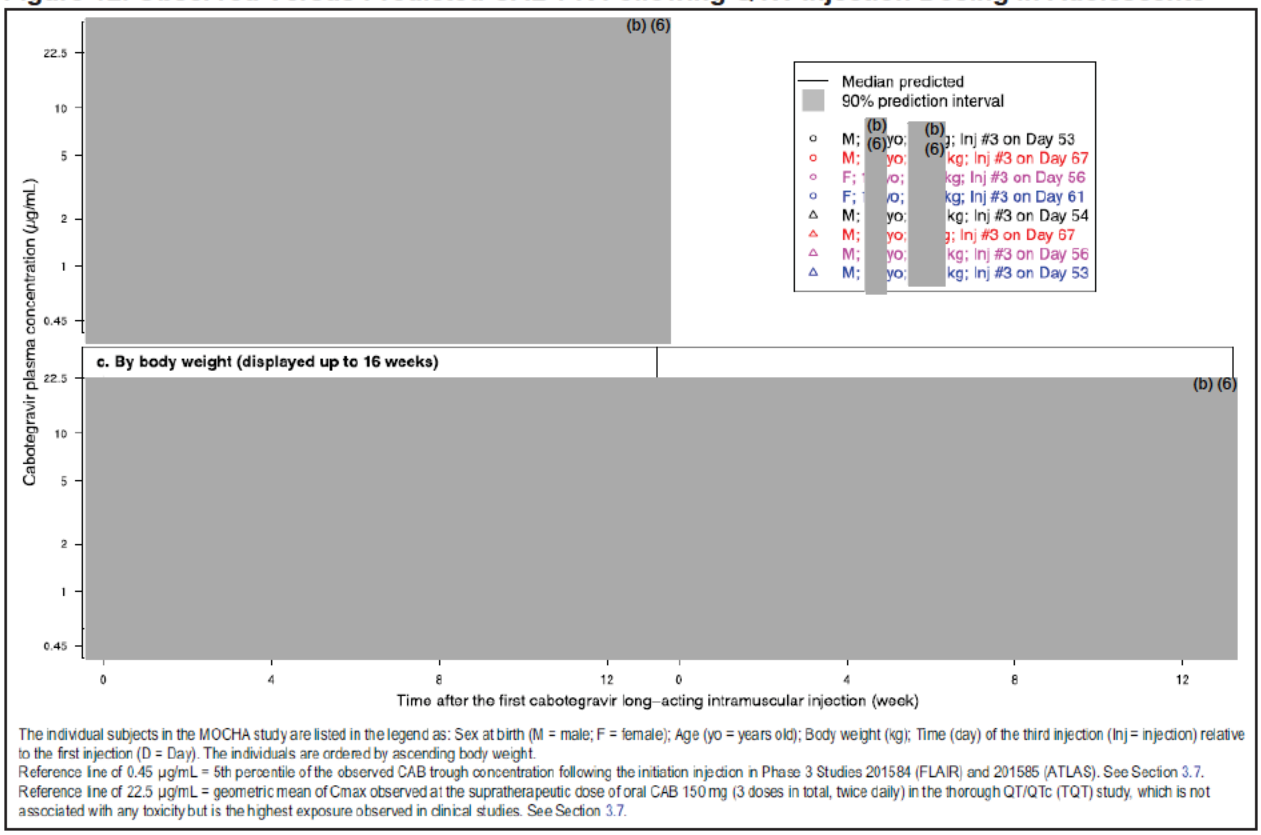
The individual subjects in the MOCHA study are listed in the legend as: Sex at birth (M = male; F = female); Age (yo = years old); Body weight (kg). The individuals are ordered by ascending body weight.

Reference line of 0.45 µg/mL = 5th percentile of the observed CAB trough concentration following the initiation injection in Phase 3 Studies 201584 (FLAIR) and 201585 (ATLAS). See Section 3.7.

Reference line of 22.5 µg/mL = geometric mean of Cmax observed at the supratherapeutic dose of oral CAB 150 mg (3 doses in total, twice daily) in the thorough QT/QTc (TQT) study, which is not associated with any toxicity but is the highest exposure observed in clinical studies. See Section 3.7.

Source: NDA 212888, SN 0192.

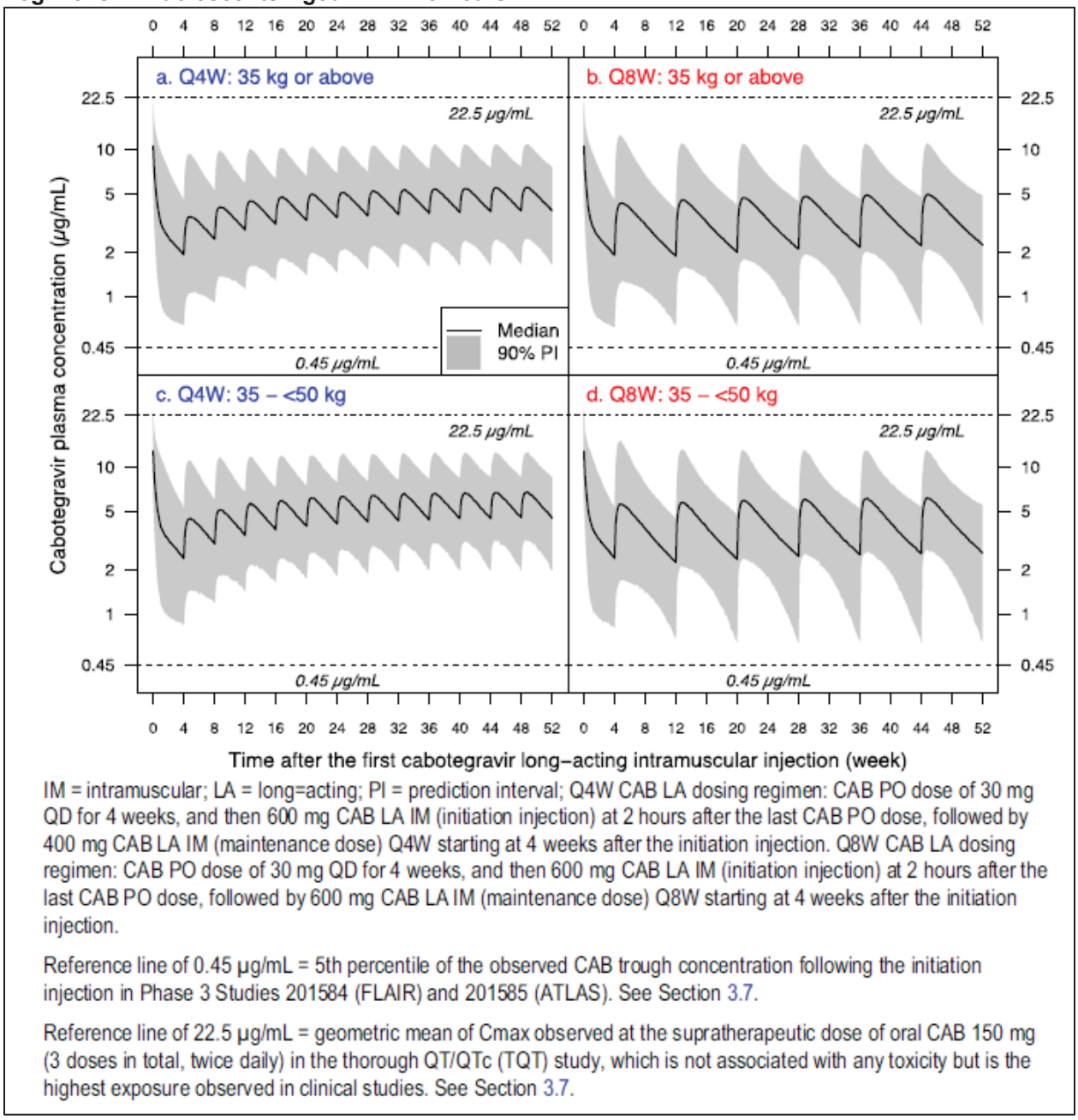
Figure 12. Observed Versus Predicted CAB PK Following Q4W Injection Dosing in Adolescents



The individual subjects in the MOCHA study are listed in the legend as: Sex at birth (M = male; F = female); Age (yo = years old); Body weight (kg); Time (day) of the third injection (Inj = injection) relative to the first injection (D = Day). The individuals are ordered by ascending body weight.
Reference line of 0.45 µg/mL = 5th percentile of the observed CAB trough concentration following the initiation injection in Phase 3 Studies 201584 (FLAIR) and 201585 (ATLAS). See Section 3.7.
Reference line of 22.5 µg/mL = geometric mean of Cmax observed at the supratherapeutic dose of oral CAB 150 mg (3 doses in total, twice daily) in the thorough QT/QTc (TQT) study, which is not associated with any toxicity but is the highest exposure observed in clinical studies. See Section 3.7.

Source: NDA 212888, SN 0192.

Figure 13. Simulated CAB Concentration Vs. Time Profiles Following CAB Q4W and Q8W Regimens in Adolescents Aged 12 – <18 Years



IM = intramuscular; LA = long=acting; PI = prediction interval; Q4W CAB LA dosing regimen: CAB PO dose of 30 mg QD for 4 weeks, and then 600 mg CAB LA IM (initiation injection) at 2 hours after the last CAB PO dose, followed by 400 mg CAB LA IM (maintenance dose) Q4W starting at 4 weeks after the initiation injection. Q8W CAB LA dosing regimen: CAB PO dose of 30 mg QD for 4 weeks, and then 600 mg CAB LA IM (initiation injection) at 2 hours after the last CAB PO dose, followed by 600 mg CAB LA IM (maintenance dose) Q8W starting at 4 weeks after the initiation injection.

Reference line of 0.45 µg/mL = 5th percentile of the observed CAB trough concentration following the initiation injection in Phase 3 Studies 201584 (FLAIR) and 201585 (ATLAS). See Section 3.7.

Reference line of 22.5 µg/mL = geometric mean of Cmax observed at the supratherapeutic dose of oral CAB 150 mg (3 doses in total, twice daily) in the thorough QT/QTc (TQT) study, which is not associated with any toxicity but is the highest exposure observed in clinical studies. See Section 3.7.

Source: NDA 215499, SN 0002, report 2021N462341_00.

Table 65. CAB Exposures in Adolescents (Aged 12-<18 Years of Age) Following OLI and Q4W or Q8W Injection Dosin

Dosing Interval	Statistics	Body Weight ≥35 kg				Body Weight 35 – <50 kg			
		AUC(0-τ) (µg × hr/mL)	C_{max} (µg/mL)	Cτ (µg/mL)	T_{max} Unit [a]	AUC(0-τ) (µg × hr/mL)	C_{max} (µg/mL)	Cτ (µg/mL)	T_{max} Unit [a]
30 mg PO QD SS	Geomean (95% CI)	193 (192,194)	14.38 (14.32,14.45)	5.79 (5.75,5.82)	2.5 [b] (0,24)	230 (229,232)	17.41 (17.3,17.52)	6.8 (6.73,6.87)	2.5 (0,24)
	Median [90% PI]	193 [106-346]	14.47 [8.02-25.54]	5.94 [2.48-12.57]	2.5 [1-6]	231 [136-393]	17.41 [10.54-28.6]	6.99 [3.04-14.21]	2.5 [1-6]
CAB LA Initiation Injection [c]	Geomean (95% CI)	2123 (2109,2138)	11.15 (11.09,11.21)	1.84 (1.82,1.85)	0 [b] (0,384)	2636 (2608,2663)	13.56 (13.46,13.67)	2.28 (2.25,2.3)	0 (0,384)
	Median [90% PI]	2142 [881-4938]	11.24 [5.63-21.5]	1.93 [0.64-4.52]	0 [0-72]	2668 [1164-5815]	13.67 [7.38-24.5]	2.39 [0.85-5.13]	0 [0-96]
Q4W [d] CAB LA SS [e]	Geomean (95% CI)	3222 (3209,3236)	7.88 (7.84,7.91)	3.65 (3.63,3.67)	8 [b] (0,28)	3887 (3865,3910)	9.6 (9.54,9.67)	4.31 (4.27,4.35)	7 (0,28)
	Median [90% PI]	3246 [1879-5406]	7.93 [4.41-13.81]	3.77 [1.63-7.49]	8 [2-22]	3897 [2471-6070]	9.62 [5.82-15.63]	4.47 [1.98-8.44]	7 [2-21]
Q8W [f] CAB LA SS [g]	Geomean (95% CI)	4871 (4850,4892)	7.23 (7.19,7.27)	2.01 (1.99,2.03)	9 [b] (1,56)	5867 (5833,5902)	8.94 (8.87,9.01)	2.28 (2.24,2.31)	9 (1,56)
	Median [90% PI]	4900 [2827-8232]	7.2 [3.76-14.12]	2.21 [0.64-4.73]	9 [3-28]	5868 [3687-9223]	8.89 [4.94-16.55]	2.57 [0.63-5.41]	9 [3-26]

90% PI = 90% prediction interval, i.e., 5th-95th percentile; AUC(0-τ) = area under concentration-versus-time curve from time 0 to the end of the dosing interval; Cτ = plasma concentration at the end of the dosing interval; C_{max} = maximum plasma concentration; CAB = cabotegravir; CI = confidence interval; Geomean = geometric mean; IM = intramuscular; LA = acting-acting; PO = oral; QD = daily; SS = steady state; T_{max} = time to reach maximum plasma concentration.

a. Unit = hr for CAB PO and CAB LA Initiation Injection; Unit = day for CAB LA SS (Q4W and Q8W).
b. Median (minimum, maximum).
c. C_{max} and T_{max} following CAB LA initiation injection is predominantly determined by the last oral dose instead of the LA injection.
d. Q4W CAB LA dosing regimen: CAB PO dose of 30 mg QD for 4 weeks, and then 600 mg CAB LA IM (initiation injection) at 2 hours after the last CAB PO dose, followed by 400 mg CAB LA IM (maintenance dose) Q4W starting at 4 weeks after the initiation injection.
e. Q4W SS: 11th CAB LA IM Injection (40-44 weeks after initiation injection)
f. Q8W CAB LA dosing regimen: CAB PO dose of 30 mg QD for 4 weeks, and then 600 mg CAB LA IM (initiation injection) at 2 hours after the last CAB PO dose, followed by 600 mg CAB LA IM (maintenance dose) Q8W starting at 4 weeks after the initiation injection.
g. Q8W SS: 6th CAB LA IM Injection (36-44 weeks after initiation injection)

Source: NDA 212888, SN 0192.

15. Trial Design: Additional Information and Assessment

15.1. Trial 201738/HPTN 083

Protocol Overview and Conduct

Table 66. Protocol Overview and Conduct, Trial HPTN 083

Applicant	**ViiV Healthcare**
Drug name	Cabotegravir (CAB)
Indication	Pre-exposure prophylaxis of HIV-1 infection (PrEP)
Protocol title	A Phase 2b/3 Double-Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men
Source of information	Protocol version 4.0 dated Feb 10, 2021, CSR dated Apr 13, 2021
Trial identifiers	
Protocol number:	201738
Clinical phase:	2b/3
EudraCT number:	N/A
Other codes:	Not applicable
IND number:	122,744
ClinicalTrial.gov identifier:	NCT02720094
Ethics	The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board, in accordance with the ICH GCP and applicable country-specific requirements, including US 21 CFR 312.3(b) for constitution of independent ethics committees.
Trial centers	This was a multicenter study conducted at 43 HPTN-affiliated centers in: United States (27 centers), Peru (5 centers), Brazil (4 centers), Argentina (2 centers), Thailand (3 centers), Vietnam (1 center), and South Africa (1 center).
Collaboration	The study was conducted by the HIV-1 Prevention Trials Network (HPTN) under sponsorship of the Division of Acquired Immunodeficiency Syndrome (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID)/ National Institutes of Health (NIH). Study drug was provided by ViiV Healthcare and Gilead Sciences. Additional funding support was provided by ViiV Healthcare.

Source: Applicant table.
Abbreviations: CFR, Code of Federal Regulations; GCP, good clinical practice; ICH, International Council for Harmonisation

Design

Table 67. Design, Trial HPTN 083

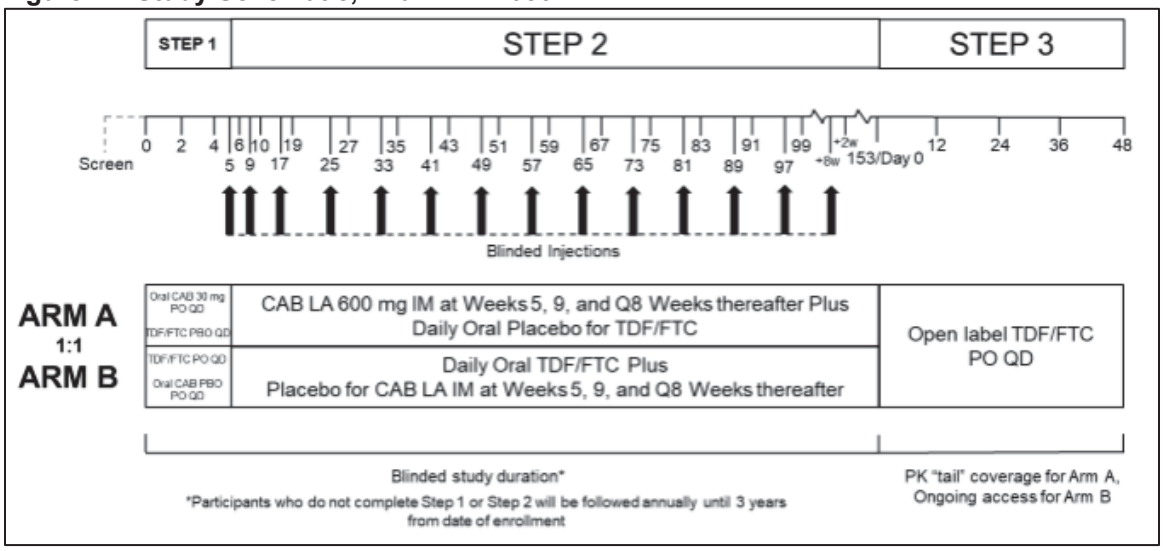
Planned Duration of Main Phase	153 Weeks (Step 1 and Step 2 of the Blinded Phase)
Planned duration of extension phase	48 weeks (Step 3 / open-label phase)
Trial status	Ongoing
Date of database lock	Dec 16, 2020
Other important dates	Early termination of the blinded phase of study (last subject last visit [LSLV] aligned with final Data Safety Monitoring Board [DSMB] meeting): May 14, 2020 (data cutoff) Protocol version 3.0 dated October 2019 was in effect during time of data cutoff (May 14, 2020) Protocol version 4.0 dated February 2021 (open-label phase of study) CSR:Apr 13, 2021

Source: Applicant table. Copyright 2021 the ViiV Healthcare group of companies. All rights reserved. Unauthorized copying or use of this information is prohibited.

This study was a phase 2b/3, multisite, double-blind, two-arm, randomized (1:1), controlled noninferiority (NI) study in HIV-uninfected MSM and TGW who have sex with men.

For details regarding treatment groups, see Treatment Groups.

Figure 14. Study Schematic, Trial HPTN 083



Source: Applicant figure. Copyright 2021 the ViiV Healthcare group of companies. All rights reserved. Unauthorized copying or use of this information is prohibited.

Objectives in Base Study

Primary Objective

- To compare HIV-1 incidence among participants randomized to oral CAB/CAB LA (OLI and injections) versus oral tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) (Steps 1 and 2).
- To compare the safety of oral CAB/CAB LA versus oral TDF/FTC (Steps 1 and 2).

Secondary Objective

- To compare HIV-1 incidence among participants who received CAB LA injections versus oral TDF/FTC in Step 2 (each step independently and all steps in aggregate).
- To compare HIV-1 incidence among participants who received CAB LA injections versus oral TDF/FTC (Steps 1, 2, and 3 combined).
- To compare HIV-1 incidence among participants who received CAB LA injections versus oral TDF/FTC (Step 3 only, descriptive).
- To estimate the change in hazard of HIV-1 acquisition between CAB and oral TDF/FTC strategies (Arm A and Arm B) as participants progressed from Step 2 to Step 3.
- To compare HIV-1 incidence among the subgroups of participants who received oral CAB/CAB LA versus oral TDF/FTC by region, age, race, ethnicity, baseline risk, and gender identity.
- To compare changes in renal function, liver function, and bone mineral density (BMD) among participants who received oral CAB/CAB LA versus oral TDF/FTC.
- To evaluate and compare rates of HIV-1 drug resistance among participants who acquired HIV-1 infection during the study among participants receiving oral CAB/CAB LA versus oral TDF/FTC.
- To compare the acceptability of and preferences for CAB LA versus oral TDF/FTC.
- To compare changes in weight, blood pressure, pulse, fasting glucose, and fasting lipids among participants who received oral CAB/CAB LA versus oral TDF/FTC.

Tertiary Objectives

- To examine the association between levels of adherence and HIV-1 incidence.
- To compare and describe the rates, patterns, and correlates of adherence to CAB LA versus oral TDF/FTC, in aggregate and by psychosocial/demographic variables.
- To estimate changes in sexual-risk behavior as measured by self-report and rates of incidence gonorrhea, chlamydia, and syphilis in the study population.
- To compare the resource utilization and programmatic costs of long-acting injectable PrEP versus daily oral PrEP versus no PrEP for HIV-1 uninfected MSM and TGW in the United States, Brazil, and South Africa.
- To use mathematical simulation to project the short- and long-term clinical impact, cost projections, budgetary impact, and incremental cost-effectiveness of long-acting injectable PrEP versus daily oral PrEP versus no PrEP for HIV-1 uninfected MSM and TGW in the United States, Brazil, and South Africa.

Exploratory Objectives

- To perform secondary laboratory assessments that may include evaluation of factors related to HIV-1 infection, hepatitis infection, or other infections; ARV drug use;

pharmacogenomics; characterization of HIV-1 in infected participants; and evaluation of laboratory assays related to the study objectives.

- To explore possible drug-drug interactions between cross-sex hormone therapy and CAB and TDF/FTC in a subset of TGW taking commonly prescribed cross-sex hormone therapy regimens.

Selection of Trial Population

Key Inclusion Criteria

- MSM and TGW, 18 years or older at the time of screening (male at birth)
- At high risk for sexually acquiring HIV-1 infection based on self-report of at least one of the following:
  - Any condomless receptive anal intercourse in the 6 months prior to enrollment (condomless anal intercourse within monogamous HIV-1 seronegative concordant relationship does not meet this criterion)
  - More than five partners in the 6 months prior to enrollment (regardless of condom use and HIV-1 serostatus, as reported by the enrollee)
  - Any stimulant drug use in the 6 months prior to enrollment
  - Rectal or urethral gonorrhea or chlamydia or incident syphilis in the 6 months prior to enrollment
  - SexPro score of ≤16 (U.S. sites only)
- In general good health, as evidenced by the following laboratory values, which must be from specimens obtained within 45 days prior to study enrollment:
  - Nonreactive / negative HIV-1 test results*
  - Hemoglobin >11 g/dL
  - Absolute neutrophil count >750 cells/mm^3
  - Platelet count ≥100,000/mm^3
  - Calculated creatinine clearance ≥60 mL/minute using the Cockcroft-Gault equation (use sex at birth for calculation)
    - Although not protocol exclusionary, sites should carefully consider the advisability of enrolling participants with calculated creatinine clearance between 60-70 mL/min, as limited changes in creatinine clearance during study conduct will lead to protocol-mandated product holds and may alter the risk-benefit consideration of study participation
  - Alanine aminotransferase (ALT) <2 times the upper limit of normal (ULN)
  - Total bilirubin <2.5 times ULN
  - Hepatitis B virus surface antigen negative
  - Hepatitis C virus Ab negative
  - No Grade 3 or higher laboratory abnormalities on any laboratory tests obtained at screening, including tests obtained as part of a panel of tests ordered to obtain the protocol-required laboratory test results.

*All HIV-1 test results from the screening visit must be obtained and must all be negative/nonreactive. This includes testing for acute HIV-1 infection, which must be performed

within 14 days of enrollment. In addition, at least one HIV-1 test result obtained at the enrollment visit must be obtained prior to provision of study product and must be negative/nonreactive. Individuals who have one or more reactive or positive HIV-1 test results will not be enrolled, even if subsequent confirmatory testing indicates that they are not HIV-1-infected.

Key Exclusion Criteria

- One or more reactive or positive HIV-1 test result at screening or enrollment, even if HIV-1 infection was not confirmed
- Past or current participation in HIV-1 vaccine trial. An exception was to be made for participants that could provide documentation of receipt of placebo (not active arm). Note: Past participation in a monoclonal antibody study was not exclusionary
- Clinically significant cardiovascular disease, as defined by history/evidence of symptomatic arrhythmia, angina/ischemia, coronary artery bypass grafting surgery or percutaneous transluminal coronary angioplasty, or any clinically significant cardiac disease
- Inflammatory skin conditions that compromised the safety of intramuscular (IM) injections, per the discretion of the Investigator of Record. Mild skin conditions may not be exclusionary at the discretion of the Investigator of Record or designee in consultation with the Clinical Management Committee (CMC)
- Had a tattoo or other dermatological condition overlying the buttock region which in the opinion of the IoR or designee, in consultation with the CMC, may interfere with interpretation of injection site reactions (ISRs)
- Current or chronic history of liver disease (e.g., nonalcoholic or alcoholic steatohepatitis) or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome, asymptomatic gallstones, or cholecystectomy)
- Coagulopathy (primary or iatrogenic) which would contraindicate IM injection (concomitant anticoagulant or antiplatelet therapy use should be discussed with the CMC)
- Active or planned use of prohibited medications (provided by self-report or obtained from medical history or medical records). In particular, future use of TDF/FTC at any point during the study
- Known or suspected allergy to study product components (active or placebo), including egg or soy products (egg and soy products are contained in Intralipid)
- Surgically-placed or injected silicone/industrial product buttock implants or fillers, per self-report
- History of seizure disorder, per self-report
- QTc interval (B or F) >500 msec

Hypotheses

This study was designed to evaluate the safety and efficacy of CAB LA for PrEP in HIV-uninfected MSM and TGW who have sex with men. In this NI trial, the null hypothesis was hazard ratio (HR)=1.23 and the design alternative was HR =0.75.

Key considerations for the analyses (sample size, analysis populations, and planned analysis time points) are highlighted in the following sections. Further descriptions of the primary analysis and of other analyses to evaluate study objectives are also included.

Treatment Groups

Eligible participants were randomized 1:1 to one of two arms and moved through the following steps (active drugs are shown in **bold text**):

Step 1

Arm A – **Daily oral CAB** (30-mg tablets) and oral TDF/FTC placebo for up to 5 weeks*

*Note: To allow for any delays in return of Week 4 testing results.

Arm B – **Daily oral TDF/FTC** (300 mg/200 mg fixed-dose combination tablets) and oral CAB placebo for 5 weeks

Participants who became HIV-infected during Step 1 of the study permanently discontinued study product and were terminated from the study and referred for HIV-1 related care.

Step 2

Arm A – **CAB LA** (600 mg as a single IM injection at two time points 4 weeks apart and Q8W thereafter) and daily oral TDF/FTC placebo to Week 153

Arm B – **Daily oral TDF/FTC** (300/200 mg fixed-dose combination tablets) and IM placebo at two time points 4 weeks apart and Q8W thereafter (identical volume as active injectable product in Arm A) to Week 153

Participants who became HIV-1-infected during Step 2 of the study permanently discontinued study product, were referred for immediate suppressive antiretroviral therapy (ART), and were followed at quarterly intervals for 52 weeks after their last injection prior to diagnosis of HIV-1 in order to test for safety parameters, as well as CD4 cell count and HIV-1 viral load. After 52 weeks, they were terminated from the study and transitioned to continued HIV-1-related care.

Step 3

Both arms: **Open-label daily oral TDF/FTC** was offered at Week 153 (last day of Step 2) /Day 0 (first day of Step 3) and continued for 48 weeks.

Note: Any participant who received at least one injection and discontinued injections prior to Week 153 was offered open-label TDF/FTC (Step 3 regimen) for 48 weeks, provided there were no clinical contraindications. For the purposes of this report, this was defined as **Early Step 3.**

All participants were transitioned to locally-available HIV-1 prevention services, including services for PrEP, if available, at the end of their participation in the study, or if they transitioned

to annual visits in Step 1 or Step 2, or if at the discretion of the primary care physician, they transitioned to Step 3 on study but off study-provided TDF/FTC.

Endpoints and Definitions

Primary Endpoints

- Efficacy endpoint: Number of documented incident HIV-1 infections in Steps 1 and 2
- Safety endpoint: Grade 2 or higher clinical and laboratory adverse events (AEs)

Secondary Endpoints

- Number of documented incident HIV-1 infections in Step 2
- Number of documented incident HIV-1 infections in Steps 1, 2, and 3
- Number of documented incident HIV-1 infections in Steps 3
- Number of documented incident HIV-1 infections in Steps 2 and 3
- Kidney function as measured by: changes from baseline in creatinine and creatinine clearance
- Liver function as measured by: changes from baseline and Grade 3 or 4 liver-related AEs (laboratory assessment of ALT, aspartate aminotransferase [AST], total bilirubin, creatine phosphokinase [CPK], or clinical assessment of jaundice/icterus)
- BMD (DXA (dual x-ray absorptiometry) subset) as measured by: Changes in Z-score from baseline and DXA criteria for osteopenia and osteoporosis
- Resistance mutations to study products (including but not limited to K65R, M184V/L, Q148R) among seroconverters
- Acceptability scale assessments
- Weight, blood pressure, pulse, fasting glucose, and fasting lipids

Tertiary Endpoints

- Adherence to study product during Step 2: For CAB LA/placebo CAB LA scheduled injections received; for TDF/FTC/placebo TDF/FTC pill dispensing
- Plasma and/or dried blood spot (DBS) levels of TDF in participants randomized to TDF/FTC
- Number of sexual partners (primary and nonprimary), numbers of coital acts, number of noncondom protected anal intercourse acts (insertive and receptive)
- Sexually transmitted infections (STIs) (rectal and urinary gonorrhea/chlamydia, syphilis [adjudicated])
- Resource utilization: Clinical visits, acuity visits (related to toxicity), hospital days (related to toxicity), standard laboratory monitoring, laboratory/radiography events (related to toxicity)

- Cost-effectiveness: 1-5 year budgetary impact, lifetime expectancy, lifetime costs projections and incremental cost-effectiveness, stratified by country

Interim Analysis

No interim analyses beyond the Data Safety Monitoring Board (DSMB) analyses were conducted.

Data Monitoring Committee

Formal interim statistical analyses were planned for three time points during the trial, with analysis times corresponding to approximately when 25%, 50%, and 75% of the estimated total number of HIV-1 infections had been observed. Interim analysis results were provided to the DSMB at the scheduled DSMB meeting immediately following the time each interim number of events had been observed, or at other time requested by the protocol team or DSMB. The DSMB received updated numbers of infections observed at each DSMB meeting.

The interim monitoring analyses were initially planned to monitor the trial for early stopping based on the interim monitoring boundary for superiority, or early evidence that oral CAB/CAB LA is definitively more effective than oral TDF/FTC. In light of a potential disruption to the dispensing of study drug caused by COVID-19 beginning in March 2020, the interim monitoring guidance was changed to recommend early stopping based on crossing the NI boundary, i.e., the O'Brien-Fleming boundary for NI. The primary endpoint was time to detection of HIV-1 infection (time from randomization to midpoint between last HIV-1 negative and first detection). In accordance with intention-to-treat principles all participants were classified into the study arm to which they were randomized. For study participants who did not acquire HIV-1 infection, study time was censored at the most recent HIV-1 test. Censoring was treated as uninformative.

Endpoint Adjudication Committee

All reactive/positive HIV-1 test results were reviewed by an independent HIV Endpoint Adjudication Committee whose responsibility was to determine whether the test results met the primary endpoint of the study of HIV-1 infection.

Sample Size Considerations

Sample Size Assumptions

The number of enrolled participants needed to observe the target number of HIV-1 infections depends on the background HIV-1 incidence in the study populations, the efficacy of CAB LA and TDF/FTC in these populations, the dropout rate, and the study duration. Assuming (a) annual HIV-1 incidence for the TDF/FTC arm was 2.0%; (b) CAB LA was 25% more protective than TDF/FTC; and (c) the annual dropout rate was 7.5%, approximately 5,000 individuals will be needed to enroll and be followed for an average of 2.5 years (refer to Section 7.6 of the protocol for power calculations).

Rationale for NI Margin

Assuming CAB LA was 25% more effective than TDF/FTC in this treatment population, approximately 172 observed HIV-1 infections would provide 90% power to rule out a NI margin of HR =1.23, with type-I error alpha =0.025. The M1 margin represents the known benefit of the active control (TDF/FTC), and was defined as the lower limit of the 95% confidence interval (CI) around the placebo versus active-control HR estimate (1.39, based on the meta-analysis). The M2 margin was defined as the reduced bound designed to preserve a clinically acceptable amount of the benefit provided by the active control. Following an accepted convention, M2 was set to be 1.23, defined as 50% of M1 (on the log scale in the case of HRs). Once the stated number of HIV-1 infections had been observed, NI would be established if the estimated CAB LA versus TDF/FTC HR point estimate was approximately 0.90 or less (indicating a 10% or better advantage of CAB LA over TDF/FTC), and superiority would be established if the HR point estimate was approximately 0.74 or less (indicating a 26% or better advantage of CAB LA over TDF/FTC). The power to detect superiority was 47%.

Response Rate Assumptions

Not applicable.

Analysis Population and Timepoint Description

Table 68. Analysis Population and Timepoint Description, Trial HPTN 083

Population	Definition / Criteria
ITT (intent-to-treat)	• All participants who were randomized, excluding those who were inappropriately enrolled.
mITT (modified intent-to-treat)	• The ITT population, excluding those who were found to be HIV-1 infected at randomization. Analysis period: Primary analysis follow-up data included study time through the completion of the blinded injection phase of study follow-up (i.e., Week 153 or the study-wide transition to Step 3, or end of the blinded phase of the study, whichever occurred first). Per the ITT principle, person time and endpoint events were included in the primary analysis regardless of whether participants remained on their blinded study product, including when participants moved to open-label TDF/FTC (Step 3) early.
PP (per protocol)	• The mITT population excluding all participants with protocol violations that were judged to be exclusionary from the per-protocol population.
Injection (Step 2) efficacy population	• The mITT population who received at least one injection and were uninfected at the time of the first injection. Analysis period: Follow-up time included primary analysis study time from the time of the first injection through the completion of the blinded injection phase of study follow-up.
Step 3 population	All mITT participants who were uninfected at the start of Step 3 follow-up (i.e., the Week 153/ study-wide transition to Step 3).
Safety population (primary analysis)	All ITT participants who received any oral or injectable product. All safety events occurring on study were reported. Step 1 AEs included all AEs occurring until the first injection date, or 120 days post randomization, whichever occurred first.

Population	Definition / Criteria
Injection (Step 2) safety population	All safety population participants who received at least one injection. Step 2 safety included all AEs occurring from the first injection date through 48 weeks after the last injection.
Longitudinal PK CAB concentration population	A longitudinal evaluation of CAB PK in the CAB arm was conducted in approximately 200 participants who received all injections up through Week 57, selected with the following regional distribution • 5% U.S. sites Non-African-American (10 participants) • 5% U.S. sites African-American (10 participants) • 40% Asia (80 participants; 50% TGW using gender affirming hormonal therapy/cross-sex hormonal therapy) • 40% Latin America (80 participants, 50% TGW using gender affirming hormonal therapy/cross-sex hormonal therapy) • 10% Africa (20 participants) This population was used for the CAB concentration listing and to enhance the population represented in the global modelling of CAB-LA PK.
TDF/FTC adherence population	Cohort of approximately 400 participants randomly selected at Baseline from the oral TDF/FTC arm.
Seroconverters	• *Primary Seroconverter Population* – All ITT participants who were HIV-1-uninfected at randomization and acquired HIV-1 infection during the primary analysis follow-up. • *Enrollment Seroconverter Population* – All ITT participants who were determined to be HIV-infected at randomization.

Source: Applicant table.

Analysis Description

Primary Efficacy Analysis Description

Modified intent-to-treat (mITT): An mITT analysis was used as the primary assessment for the efficacy comparison, where participants determined to be HIV-1 infected prior to randomization were omitted from the analysis. The HIV-1 incidence rate was calculated as the total number of participants with confirmed incident HIV-1 infection during study follow-up of Step 1, Step 2 (including time off randomized study product) up through 3 years from enrollment, divided by the person-years (PY) accumulated in each arm. 95% CIs were calculated based on Poisson distribution assumptions.

Treatment efficacy was estimated as TE =1 - HR. The hazard ratio comparing CAB LA versus TDF/FTC and 95% CIs was estimated using Cox proportional hazards regression with treatment arm as the only covariate, stratified by region and adjusted for early stopping.

On blinded study product (OBSP): An on blinded study product estimate of treatment efficacy was conducted as a secondary analysis in the NI context of active control, as a verification that a similar HR estimate was obtained in participants who were HIV-uninfected at the time of the first injection, restricted to follow-up compliant to the injection schedule by censoring when a participant did not receive blinded injection study product on time. Compliance was defined as

receiving the second injection within 6 weeks of the first injection and all subsequent injections within 10 weeks of the prior injection.

Per protocol: A per protocol estimate of treatment efficacy, excluding participants with major protocol violations, or participant time after a major protocol violation was planned if the number of participants affected exceeded 2% of the enrolled population. The prespecified criteria were not met to perform this analysis.

Sensitivity and Supportive Statistical Analyses Description

Safety Analysis

Safety data were analyzed using the data from the safety populations.

The primary safety objective to compare the safety of oral CAB/CAB LA versus oral TDF/FTC (Steps 1 and 2) was assessed using the primary safety endpoint of Grade 2 or higher clinical and laboratory AEs throughout the study (Step 1, 2, 3, and annual follow-up) and the summaries of OBSP AEs in Step 1 and Step 2.

Injection site reactions: The number and percentage of participants experiencing local reactions to the injections were tabulated by severity and treatment arm and the percentages displayed graphically by arm. For a given local reaction type, each participant's reaction was counted once under the maximum severity for all injection visits. In addition, to the individual reaction types, the maximum severity of local pain or tenderness, induration or erythema, and of systemic symptoms was calculated.

AEs and serious adverse events (SAEs): AEs were summarized using Medical Dictionary for Regulatory Activities (MedDRA, Version 23.1) system organ class and preferred terms (PTs). Tables show by treatment arm the number and percentage of participants experiencing an AE within a system organ class and within preferred term category by severity (grade). For the calculations in these tables, a participant with multiple AEs within a PT category was counted once under the maximum severity. Formal statistical testing comparing arms was not planned since interpretation of differences must rely heavily upon clinical judgment. A listing of SAEs reported to the Division of Acquired Immunodeficiency Syndrome (DAIDS) Regulatory Support Center (RSC) safety office provided details of the events including severity, time between onset and last dosing, and cumulative number of doses received. SAE case narratives were from GlaxoSmithKline/ViiV and were based on SAE source information provided by RSC and reconciliation of certain fields within the clinical study database.

HPTN Hepatic Adjudication Committee: Cases meeting liver stopping criteria were evaluated by an independent hepatic adjudication committee operating under an adjudication committee charter.

Local laboratory values: Box plots of local laboratory values for maximum liver chemistries (AST, ALT, alkaline phosphatase, and bilirubin) from Baseline were generated by treatment arm. Each box plot showed the first quartile, the median, and the third quartile. Outliers (values outside the box plot) were plotted. If appropriate, horizontal lines representing boundaries for abnormal values were plotted. The number (percentage) of participants with local laboratory values recorded as meeting Grade 2 AE criteria or above as specified in the DAIDS AE Grading Table were tabulated by treatment arm for follow-up time points. Reportable clinical laboratory

abnormalities without an associated clinical diagnosis were also included in the tabulation of AEs described above.

Summary of Study Phases (Steps) and Associated Analyses

Table 69. Summary of Study Phases (Steps) and Associated Analyses, Trial HPTN 083

Study Phase	Efficacy Analysis	Safety Analysis
Step 1 (blinded oral lead-in phase)	Efficacy analysis: Step 1 included time between randomization and the first injection date or study product discontinuation and/or study termination date, whichever occurred first.	Safety analysis: Step 1 included AE(s) with onset date between the date of randomization and the first injection date, or 120 days post randomization, whichever occurred first. On blinded study product safety analysis: Step 1 included AE(s) with onset date between the date of randomization and the first injection date, the date of study product discontinuation/study termination, OR 120 days postrandomization (whichever occurred first).
Step 2 (blinded injection phase)	Efficacy analysis Step 2 included time from the first injection through the completion of the blinded injection phase of study follow-up. On blinded study product efficacy analysis: Step 2 included time from the first injection up to the first time the blinded injection was not given or delayed for any reason (refer to OBSP censoring explanation).	Safety analysis: Step 2 included AE(s) with an onset date on or after the date of first injection through 48 weeks after the last injection. On blinded study product safety analysis: Step 2 included AE(s) with onset date on or after the first injection through 6 weeks (if only 1 injection is given) or 10 weeks (if 2 or more injections are given) after the last blinded injection OR the first open-label pill dispensation on or after the first Step 3 Start Date (Open-label TDF/FTC), whichever occurred first.
Early Step 3 Discontinued study product during Step 2 and entered open-label TDF/FTC for 48 weeks post last injection.	This data was considered as part of Step 2 for the Step 1 and Step 2 primary efficacy analyses and the Step 2 efficacy analysis. It was excluded from the OBSP efficacy analysis.	This data was considered part of the Step 3 (Tail Phase) for safety analysis and was excluded from Safety OBSP.

Study Phase	Efficacy Analysis	Safety Analysis
Protocol planned transition to Step 3 : Completed Week 153 (last day of Step 2) and are offered open-label TDF/FTC for 48 weeks post last injection. Tail Phase: Early Step 3 and protocol planned transition to Step 3 terminology was used in the protocol to refer to the open-label TDF/FTC study period. For the purposes of this report, Step 3 will be referred to as the Tail Phase for safety analysis. Tail Phase includes the time from when a participant discontinues the blinded injection and continues for 48 weeks where participants are offered open - label TDF/FTC.	This data was considered as part of Step 2 for the Step 1 and Step 2 primary efficacy analyses and the Step 2 efficacy analysis if it is within 1101 days from randomization. It was excluded from the OBSP efficacy analysis.	Safety analysis The Tail Phase included AEs with onset date after the last injection through 48 weeks from the last injection. This data was excluded from the Safety OBSP analysis.
Annual follow-up No study product or open-label product are administered. Annual follow-up visits for any participant who has discontinued treatment, has not seroconverted, has completed 48 weeks open-label TDF/FTC post last injection, if needed, and has not been followed in the study for at least three years or terminated from the study.	This data was considered as part of Step 1 and Step 2 for efficacy analyses if it was within 1,101 days from randomization. It was excluded from the OBSP efficacy analysis.	This data was excluded from the Safety OBSP and Step 3 (Tail Phase) but was included in the primary safety endpoint assessing AEs throughout the study.
Throughout the study	---	Step 1, 2, 3 and annual follow-up, used for the primary safety endpoint.

On blinded study product (OBSP) efficacy analysis: To support the noninferiority hypothesis, a supportive analysis was presented using the OBSP censoring in the Injection (Step 2) Efficacy population, where study follow-up was censored when a participant did not receive blinded injection study product on time.

Censoring:
Censoring for the OBSP efficacy analysis excluded any time affected by delayed injections. Participants were censored the first time an injection was delayed, which was defined as follows:

For STEP 2:
1. Last nondelayed injection: The earliest of an injection whose subsequent injection was delayed for the first time (i.e., given >6 weeks after the Week 5 injection or >10 weeks after any other injection) or the last injection before a termination or a permanent product discontinuation.

2. For participants with a delayed injection, follow-up time was censored at the last visit with HIV-1 status determined up through 6 weeks after the Week 5 injection, if that was the last nondelayed injection, or 10 weeks after the last nondelayed injection for subsequent injections.

3. For participants with no delayed injections, analysis time was defined as for primary efficacy analysis.

Study Phase	Efficacy Analysis	Safety Analysis

OBSP safety analysis: An OBSP safety analysis was performed to assess the safety profile of blinded study product.

Censoring:
For STEP 1:
For a participant who never received an injection, AEs were censored when the onset date fell after the earliest of 120 days after randomization or at the termination or permanent product discontinuation date +1. This included AEs reported for participants who did not receive any injectable product.

1. If date of 1st injection was not missing, then Date of First Injection – 1 was used.
2. If date of 1st injection was missing but either treatment discontinuation or study termination or both were present, min (date of treatment discontinuation, date of study termination, then Step 1 Start Date +120) +1 was used.
3. If there was no treatment discontinuation or study termination and no injections were administered, then Step 1 Start Date +120 days was used.

For STEP 2:
For participants who received an injection, AE follow-up was censored after the last injection regardless of any delays in injections. If only 1 injection was given, the participant's safety events were censored at 6 weeks after the first injection, or 10 weeks after the last injection if more than 1 injection was given.

Source: Applicant table.

Other Analyses

Study Medication Satisfaction Questionnaire: The Study Medication Satisfaction Questionnaire (SMSQ) was used to assess participant tolerability of and satisfaction with the study medication. The SMSQ is a modified version of the current HIV Treatment Satisfaction Questionnaire that does not include questions pertaining to treatment, but rather study medication. The SMSQ is a 12-item self-reported scale that measures overall satisfaction with medication. Both the SMSQs (status version) and the SMSQc (change version) were utilized.

The SMSQs was administered at the following time points: Weeks 6, 10, 19, 27, 35, 43, 51, 59, 67, 75, 83, 91, 99, 107, 115, 123, 131, 139, 147, and Step 3, Day 0 if the questionnaire was not administered within the last 24 weeks. The SMSQc was administered at Week 19. See Section 7.5.8 of the statistical analysis plan (SAP) for full details of SMSQ analyses.

Sexual risk behaviors: To assess behavioral risks for HIV-1 during the study period, participants were asked about their sexual behaviors and other behavioral risks for HIV-1 via a computer assisted self-interview questionnaire which was administered at baseline (at enrollment date) and at each injection visit week (Weeks 5, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 121, and Step 3 Day 0). See Section 7.5.8 of the SAP for full details of sexual risk behaviors analyses.

Changes in Conduct of the Study or Planned Analyses

The independent DSMB recommended early termination of the blinded, randomized portion of the study on May 14, 2020, at the first planned interim analysis (i.e., 25% of the planned events) due to crossing the prespecified stopping boundary. Results indicated that a PrEP regimen containing CAB LA injected once Q8W was superior to daily oral tenofovir/emtricitabine for HIV-1 prevention among MSM and TGW who have sex with men. The DSMB recommended the blinded, randomized portion of the study be stopped early and results

released. Data summarized for this study for this report includes the blinded portion of the study only (all data up until May 14, 2020).

The SAP was amended while the blinded statistician was still blinded to individual participant randomized treatment as follows:

- The first amendment included a change from open-ended follow-up to a maximum follow-up of 3 years per participant and an increase of sample size from 4,500 to 5,000 participants.
- The second amendment was implemented following the decision to unblind the study results after the May 14, 2020, DSMB review. The blinded statistician continued to not have access to individual level data.
- The third amendment provided clarifications and updates to analysis populations and subgroups and clarified which proposed analyses will be produced for the clinical study report (CSR) versus other later exploratory analyses. The blinded statistician continued to not have access to individual level data while making this amendment.

The efficacy analyses that included Step 3 were excluded due to the timing of the blinded portion of the study stopping early. At that time, only 19 participants had entered into the protocol-defined Step 3 and therefore the efficacy analyses that included Step 3 was no longer informative. Therefore, the following endpoints were not performed for this CSR:

- Number of documented incident HIV-1 infections in Steps 1, 2, and 3
- Number of documented incident HIV-1 infections in Step 3
- Number of documented incident HIV-1 infections in Steps 2 and 3

The data for BMD was not available in time to be included in this report.

- BMD (DXA subset) as measured by: Changes in Z-score from baseline and DXA criteria for osteopenia and osteoporosis

The following tertiary endpoints will be explored later and were not included in this report:

- Resource utilization: Clinical visits, acuity visits (related to toxicity), hospital days (related to toxicity), standard laboratory monitoring, laboratory/radiography events (related to toxicity)
- Cost-effectiveness: 1-5 year budgetary impact, lifetime expectancy, lifetime costs projections and incremental cost-effectiveness, stratified by country

The following deviations from the SAP were performed after the blinded statistician had been unblinded.

- For OBSP analysis, the analysis period for the injection (Step 2) efficacy population, follow-up time included study time from randomization instead of the start of the first injection. This is a deviation from Section 6.4 of the SAP.
- The injection (Step 2) efficacy population was updated to be the mITT population who receive at least one injection and are uninfected at the time of the first injection and have at least one follow-up visit with nonmissing HIV-1 test results after first injection.

Having at least one follow-up visit with nonmissing HIV-1 test results after the first injection was not stated in the SAP Section 6.4.

- The safety population deviated from the SAP Section 6.6 to include all randomized participants who received any oral or injectable product instead of all intent-to-treat participants who received any oral or injectable product. This deviation was done to be sure to report all safety events occurring on study for all participants who received any investigational product.
- SAP did not classify the following three events as competing events. This was different from what had been reported in previous DSMB reports. The decision was made on January 20, 2021, to follow the DSMB definition for competing events. "REPORTED USE OF PROHIBITED CONCOMITANT MEDICATION," "PARTICIPANT IS CURRENTLY USING OR PLANNING TO USE PREP OR PEP," "LOW ORAL ADHERENCE ACCORDING TO PROTOCOL."
- Analysis of incidence of STIs was not detailed in SAP but was produced using similar approach to what was used in the DSMB report.
- The Kaplan-Meier plots by region were not produced due to the low event counts and since a figure was produced to support the subgroup analysis.
- Participant who might be lost to follow-up were still being counted as ongoing unless the site entered a study termination reason as “Other” with a subreason of “Lost to Follow-up.”
- Resistance data was summarized by treatment arm for all seroconverters, but they were not summarized by treatment arm for each step of the trial separately. This detail is provided in the listing.

The following items were not performed for the CSR as stated in the protocol.

- No formal comparison of the changes in renal function, liver function, and BMD was performed for the CSR among participants receiving oral CAB/CAB LA versus oral TDF/FTC as stated in the protocol.
- Box plots of local laboratory values were not generated for the CSR as described in the protocol.
- Per protocol analyses using compliance as a time dependent covariate or in the compliant cohort were not performed for the CSR.

15.2. Trial 201739/HPTN 084

Protocol Overview and Conduct

Table 70. Protocol Overview and Conduct, Trial HPTN 084

Item	Description
Applicant	ViiV Healthcare
Drug name	Cabotegravir (CAB)
Indication	Pre-exposure prophylaxis of HIV-1 infection (PrEP)
Protocol title	A Phase 3 Double-Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women
Source of information	Protocol version 2.0 dated Nov 6, 2019; CSR dated Jul 8, 2021
Trial identifiers	
Protocol number:	201739
Clinical phase:	3
EudraCT number:	Not applicable
Other codes:	Not applicable
IND number:	122,744
ClinicalTrial.gov identifier:	NCT03164564
Ethics	The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board, in accordance with the ICH GCP and applicable country-specific requirements, including U.S. 21 CFR 312.3(b) for constitution of independent ethics committees.
Trial centers	This was a multicenter study conducted at 20 HPTN-affiliated centers in: Botswana (1 center), Kenya (1 center), Malawi (2 centers), South Africa (7 centers), eSwatini [formerly Swaziland] (1 center), Uganda (3 centers), and Zimbabwe (5 centers).
Collaboration	The study was conducted by the HIV Prevention Trials Network (HPTN) under sponsorship of the Division of Acquired Immunodeficiency Syndrome (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID)/ National Institutes of Health (NIH). Study drug was provided by ViiV Healthcare and Gilead Sciences. Additional funding support was provided by ViiV Healthcare and the Bill and Melinda Gates Foundation.

Source: Applicant table.
Abbreviations: CFR, Code of Federal Regulations; CSR, clinical study report; GCP, good clinical practice; ICH, International Council for Harmonisation

Design

Table 71. Design, Trial HPTN 084

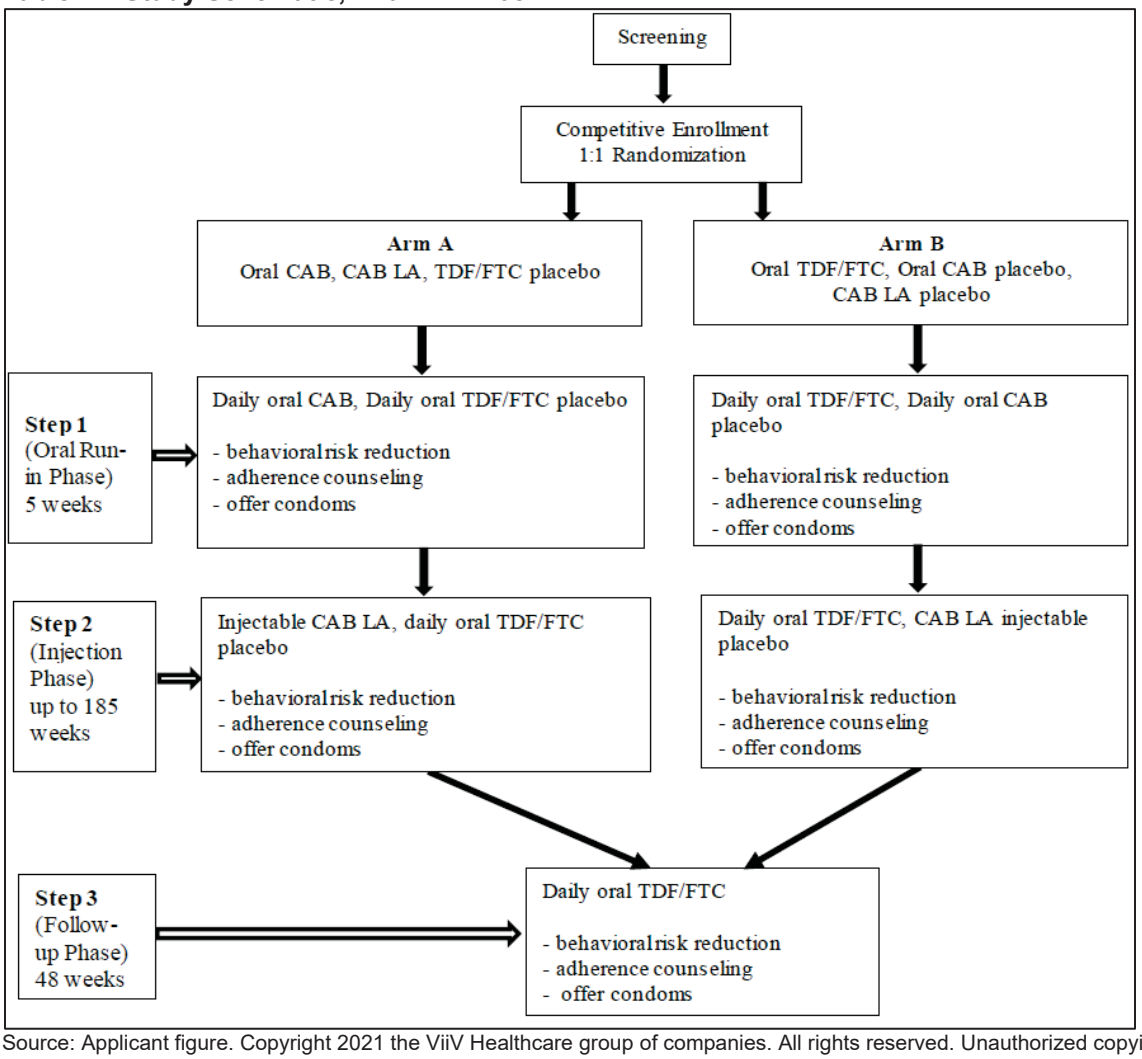
Item	Description
Planned duration of main phase	Up to 190 weeks (Step 1 and Step 2 of the blinded phase)
Planned duration of extension phase	48 weeks (Step 3 / follow-up phase)
Trial status	Ongoing
Date of database lock	Apr 16, 2021
Other important dates	Early termination of the blinded phase of study (last subject last visit [LSLV] aligned with final data safety monitoring board [DSMB] meeting): Nov 5, 2020 (data cutoff) Protocol version 1.0 dated Mar 2, 2017 Protocol version 2.0 dated Nov 6, 2019, was in effect during time of data cutoff (Nov 5, 2020) CSR: Jul 8, 2021

Source: Applicant table.

This study is an ongoing phase 3, multicenter, double-blind, two-arm, randomized (1:1), controlled superiority study of the safety and efficacy of CAB LA compared to daily oral TDF/FTC for HIV-1 prevention in a population of sexually active HIV-1-uninfected women at risk for HIV. This study has a similar design to an efficacy study in HIV-1-uninfected men who have sex with men and transgender women (HPTN 083) and will provide complementary information.

For details regarding treatment groups, see Treatment Groups.

Table 72. Study Schematic, Trial HPTN 084



Source: Applicant figure. Copyright 2021 the ViiV Healthcare group of companies. All rights reserved. Unauthorized copying or use of this information is prohibited.

Objectives in Base Study

Primary Objectives

- Efficacy: To evaluate the relative efficacy of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) versus daily oral TDF/FTC for HIV-1 prevention (Steps 1 and 2).
- Safety: To evaluate the relative safety of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) versus daily oral TDF/FTC for HIV-1 prevention (Steps 1 and 2).

Secondary Objectives

- To compare HIV-1 incidence among participants receiving oral CAB/CAB LA versus daily oral TDF/FTC (Steps 1, 2 and 3).

- To evaluate relative efficacy of oral CAB/CAB LA versus oral TDF/FTC in subgroups defined by the baseline factors of: age, herpes simplex virus-2 (HSV-2) serostatus*, contraceptive method*, and body mass index (BMI).
- To describe and model the relationship between HIV-1 incidence and drug concentration, within each arm.
- To describe the distribution and correlates of drug concentration, within each arm.
- To compare the acceptability of and preferences for CAB LA versus oral TDF/FTC.

*NOTE: HSV-2 serostatus and contraceptive method subgroup efficacy analyses are outside the scope of the CSR and will be the subject of a separate reporting effort.

Tertiary Objectives

- To estimate sexual risk behaviors, as measured by self-report and rates of incident STIs.
- To compare Grade ≥2 AE rates in women with baseline BMI </≥25 kg/m^2, within each study arm*.
- To compare differences in weight gain and BMI, by arm.
- To compare pregnancy incidence and outcomes between arms.
- To evaluate rates of HIV-1 drug resistance among participants who acquire HIV-1 infection during the study among participants receiving oral CAB/CAB LA versus oral TDF/FTC.
- To determine plasma concentrations of depot medroxyprogesterone acetate (DMPA), norethisterone enanthate (NET-EN) or etonogestrel when co-administered for contraception with study products (TDF/FTC or CAB LA)*.

*NOTE: These analyses are outside the scope of the CSR and will be the subject of a separate reporting effort.

Exploratory Objectives

- To compare the estimated programmatic cost, cost-effectiveness and disease impact indicators of CAB LA versus daily oral TDF/FTC versus no PrEP for HIV-1-uninfected women in the study sites locations.
- To perform secondary laboratory assessments that may include evaluation of factors related to HIV-1 infection, hepatitis infection, and other infections; ARV drug use; pharmacogenomics; characterization of HIV-1 in infected participants; and evaluation of laboratory assays related to the study objectives.

Selection of Trial Population

Key Inclusion Criteria

- Born female
- 18-45 years at the time of screening

- Willing and able to provide informed consent
- Willing and able to undergo all required study procedures
- Nonreactive HIV-1 test results at screening and enrollment*

*HIV-1-uninfected, based on HIV-1 test results obtained at screening and just prior to randomization at the enrollment visit. All HIV-1 test results from the screening visit were required to be obtained and be negative/nonreactive. This included testing for acute HIV-1 infection, which was performed within 14 days of enrollment. In addition, at least 1 HIV-1 test result using blood drawn at the enrollment visit was required prior to randomization into the study and had to be negative/nonreactive. Individuals who had one or more reactive or positive HIV-1 test result(s) were not enrolled, even if subsequent confirmatory testing indicated that they were not HIV-1-infected (as described in the Study Specific Procedures Manual). Those with any enrollment positive HIV-1 test result proceeded through the HIV-1 algorithm per the Study Specific Procedures Manual but were not able to receive study product regardless of subsequent test results.

- Sexually active (i.e., vaginal intercourse on a minimum of 2 separate days in the 30 days prior to screening)
- Score of ≥5 using a modified Vaginal and Oral Interventions to Control the Epidemic (VOICE) risk score* (Balkus et al. 2016).

*NOTE: Protocol version 1.0 (March 2, 2017) permitted enrollment of women who scored >2 using a modified VOICE Risk Score. Protocol version 1.0 was updated on November 6, 2019, to permit enrollment of women who scored ≥5 using a modified VOICE risk score to target women at higher risk of HIV-1 acquisition.

- No plans to relocate or travel away from the site for ≥8 consecutive weeks during study participation
- Creatinine clearance ≥60 mL/min (using Cockcroft-Gault equation) (using sex at birth for calculation)
  - Although not protocol exclusionary, sites were to carefully consider the advisability of enrolling participants with calculated creatinine clearance between 60-70 mL/min, as limited changes in creatinine clearance during study conduct could lead to protocol-mandated product holds and could alter the risk-benefit considerations of study participation
- Hepatitis B virus surface antigen negative and accepts vaccination
- ALT <2x ULN and total bilirubin ≤2.5x ULN
- Hepatitis C virus antibody negative
- If of reproductive potential (defined as premenopausal women who did not have a sterilization procedure per self-report, such as hysterectomy, bilateral oophorectomy, tubal ligation or salpingectomy), must have had a negative beta human chorionic gonadotropin pregnancy test (sensitivity of ≤25 mIU/mL) performed (and results known) on the same day as and before initiating the protocol-specified study product(s) at enrollment.

- Had documented evidence of surgical sterilization, OR documented evidence of no uterus (e.g., hysterectomy), OR agreed to use a reliable form of long acting contraception during the trial and for 52 weeks after stopping the long acting injectable, or 30 days after stopping oral study product, from the list below:
  - Intrauterine device or intrauterine system that meets <1% failure rate as stated in the product label
  - Hormone-based contraceptive that meets <1% failure rate when used consistently and correctly as stated in the product label (implants or injectables only; this excluded combined oral contraception)
- No medical condition that, in the opinion of the study investigator, would interfere with the conduct of the study (e.g., provided by self-report, or found upon medical history and examination or in available medical records)
- No alcohol or substance use that, in the opinion of the study investigator, would interfere with the conduct of the study (e.g., provided by self-report, or found upon medical history and examination or in available medical records)

Key Exclusion Criteria

- One or more reactive HIV-1 test results at screening or enrollment, even if HIV-1 infection was not confirmed
- Pregnant or currently breastfeeding, or intended to become pregnant and/or breastfeed during the study
- Co-enrollment in any other HIV-1 interventional research study (provided by self-report or other available documentation), with one exception: IMPAACT 2026* (co-enrollment in IMPAACT 2026 was permitted for participants who became pregnant)
- Current or past enrollment in an HIV-1 vaccine or broadly neutralizing antibody trial
- Current or chronic history of liver disease (e.g., nonalcoholic or alcoholic steatohepatitis) or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome, asymptomatic gallstones, or cholecystectomy)
- History of seizure disorder, per self-report
- Clinically significant cardiovascular disease, as defined by history/evidence of symptomatic arrhythmia, angina/ischemia, coronary artery bypass grafting surgery or percutaneous transluminal coronary angioplasty or any clinically significant cardiac disease
- Inflammatory skin conditions that could compromise the safety of intramuscular injections, per the discretion of the Investigator of Record. Mild skin conditions may not have been exclusionary at the discretion of the Investigator of Record or designee
- Has a tattoo or other dermatological condition overlying the buttock region which in the opinion of the Investigator of Record or designee may interfere with interpretation of ISRs
- Coagulopathy (primary or iatrogenic) which would contraindicate IM injection

- Active or planned use of prohibited medications as described in the Investigator's Brochure or listed in the Study Specific Procedures Manual (provided by self-report, or obtained from medical history or medical records)
- Known or suspected allergy to study product components (active or placebo), including egg or soy products (egg and soy products are contained in Intralipid)
- If potentially able to conceive, unwilling to adhere to long acting contraception (intrauterine device / intrauterine system , injection, or implant) with a <1% failure rate when used consistently and correctly as stated in the product package insert/ manufacturer's guidelines.

*NOTE: No participants were co-enrolled in IMPAACT 2026 due to early termination of the blinded portion of the HPTN 084 trial, which occurred before IMPAACT 2026 was implemented.

Hypotheses

This study was designed to evaluate the safety and efficacy of CAB LA for PrEP in HIV-uninfected women. The hypothesis Ho: HR =1.0 versus Ha: HR ≠ 1.0 using α =0.05 was tested.

Key considerations for the analyses (sample size, analysis populations, and planned analysis time points) are described in Sample Size Considerations and Analysis Population and Timepoint Description. Further descriptions of the primary analysis and of other analyses to evaluate study objectives are described in Analysis Description.

Treatment Groups

Eligible participants were randomized 1:1 to one of two arms and moved through the following steps (active drugs are show in **bold text**):

Step 1 – Oral Run-in Phase

- Arm A – Daily **oral CAB** and oral TDF/FTC placebo for up to 5 weeks* plus an HIV-1 prevention package including behavioral risk reduction and adherence counseling and offer of condoms.

*NOTE: Five weeks of oral CAB was supplied to monitor tolerability and safety over 4 weeks and to allow for any delays in testing results.

- Arm B – Daily **TDF/FTC** and oral CAB placebo for up to 5 weeks plus an HIV-1 prevention package including behavioral risk reduction and adherence counseling and offer of condoms.

Participants who became HIV-infected during Step 1 permanently discontinued study product and were terminated from the study and referred for HIV-related care.

Participants who had a first positive pregnancy test during Step 1 (Week 2 or Week 4) may have transitioned to Step 2 if subsequent pregnancy testing done 4 weeks after the initial positive pregnancy test determined that the participant was not pregnant and all other safety requirements for transition to Step 2 were met.

Step 2 - Injection Phase

- Arm A – Injections of **CAB LA** at two time points 4 weeks apart and every 8 weeks thereafter and daily oral TDF/FTC placebo beginning at Week 5 plus an HIV-1 prevention package including behavioral risk reduction and adherence counseling and offer of condoms. Injections were administered as 600 mg of CAB LA in one 3 mL IM injection.
- Arm B – Daily **TDF/FTC** and IM placebo (matching vehicle, identical volume as active injectable product in Arm A) beginning at Week 5 plus an HIV-1 prevention package including behavioral risk reduction and adherence counseling and offer of condoms.

Step 2 was intended to continue until the required number of endpoints (114) was reached, estimated to be 81 weeks after enrolling the last participant, or until a stopping boundary was crossed.

Participants who prematurely discontinued study product during Step 2 for any reason other than HIV-1 infection were transitioned to open-label TDF/FTC for 48 weeks during Step 2 follow-up and then retained in annual testing for the duration of Steps 2 and 3 (see description of **Step 3**).

Participants who became HIV-infected during Step 2 permanently discontinued study product, were referred for care, and were followed at quarterly intervals for approximately 48 weeks.

Confirmed Pregnancies

Participants with a positive pregnancy test required confirmation of pregnancy at a subsequent visit at least four weeks later. All pregnant participants with a confirmed positive pregnancy test (four weeks after the initial pregnancy test) were unblinded and followed by the study every 12 weeks. Regardless of the randomization assignment or point in the study, all pregnant participants were to be placed on open-label TDF/FTC at the first positive pregnancy test visit and if confirmed for the duration of the pregnancy and breastfeeding. No participant with a positive pregnancy test was to be administered CAB, CAB LA, or CAB LA placebo.

Once pregnancy outcome was reached, if the participant was not breastfeeding, she could resume unblinded study product and visits according to the schedule of evaluations (SOE). Should a participant who delivered a child during the study elect to breastfeed, she continued open-label TDF/FTC and was followed per the SOE. Once the participant finished breastfeeding, she could resume study product and visits according to the SOE. Unblinded participants had the option to return to open-label study product in their original randomization arm (either CAB LA or oral TDF/FTC).

Lapses or Discontinuations of Long-Acting Contraception

In the event of a lapse in contraception or where evidence of contraception could not be provided, participants were provided with open-label TDF/FTC for up to four weeks while pregnancy testing was performed, and pregnancy excluded. Participants could resume blinded study product once pregnancy was excluded on one or more pregnancy tests.

Participants who discontinued long acting contraception and with the potential to conceive were placed on open-label TDF/FTC for the period that they were not on long-acting contraception for up to 48 weeks or through conception and breastfeeding. Participants who resumed long-acting

contraception after a study product interruption and who did not experience a confirmed pregnancy during that period could resume blinded study product (per original randomization) following documentation of a negative pregnancy test, and where all other standard visit criteria were met.

Step 3 - Follow-Up Phase*

- Arms A and B – Open-label daily **TDF/FTC** (in order to cover the PK tail for Arm A participants) was provided no later than 8 weeks after the last injection visit, for up to 48 weeks plus an HIV-1 prevention package including behavioral risk reduction and adherence counseling and offer of condoms.

All participants were to be transitioned to locally available HIV-1 prevention services, including services for PrEP, if available, when participation in Step 3 ended.

*NOTE: The study was designed to include a Step 3 after the required number of incident HIV-1 infections had been reached. After completion of Step 3, all participants were to be transitioned to local HIV-1 prevention services. However, due to meeting prespecified stopping criteria for superiority of CAB LA to TDF/FTC, the blinded, randomized portion of the study was stopped early, at which time, no participant had been transitioned to protocol-planned Step 3.

Endpoints and Definitions

Primary Endpoints

- Efficacy endpoint: Number of documented incident HIV-1 infections in Steps 1 and 2
- Safety endpoint: Grade 2 or higher clinical and laboratory AEs

Secondary Endpoints

- Number of documented incidents HIV-1 infections in Steps 1, 2, and 3
- Number of documented incident HIV-1 infections in participants in subgroups broken down by Baseline age, HSV-2 status*, contraceptive use method*, and BMI $</\geq 25$ kg/m^2**
- Plasma concentrations of CAB in participants randomized to CAB/CAB LA
- Plasma and DBS concentrations of tenofovir/tenofovir diphosphate (TFV/TFV-DP) in a subset of participants randomized to TDF/FTC
- Survey of attitudes and willingness to use CAB LA and TDF/FTC

*NOTE: HSV-2 serostatus and contraceptive method subgroup efficacy analyses are outside the scope of the CSR and will be the subject of a separate reporting effort.

**NOTE: BMI cutoff was modified from $</\geq 25$ kg/m^2 in the protocol to $</\geq 30$ kg/m^2 in the SAP. This change was made to be consistent with the analysis and reporting of the HPTN 083 Study.

Tertiary Endpoints

- Sexual risk (number of partners, number of unprotected sex acts)

- Incident STIs (gonorrhea/chlamydia, trichomonas, syphilis)
- Grade 2 or higher clinical and laboratory AEs broken down by BMI </≥25 kg/m^2
- Weight
- Number of incident pregnancies
- Pregnancy outcomes
- Resistance mutations to study products (including but not limited to K65R, M184V/I, Q148R) among seroconverters
- Plasma concentrations of DMPA, or NET-EN, and etonogestrel when co-administered with study product (TDF/FTC or CAB LA)*

*NOTE: These analyses are outside the scope of the CSR and will be the subject of a separate reporting effort.

Interim Analyses

No interim analyses beyond the DSMB analyses were conducted.

Data Monitoring Committee

An independent DSMB met approximately every six months throughout the study to: 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress and treatment efficacy and 2) make recommendations to the study investigators and DAIDS concerning the continuation, modification, or termination of the trial. Analyses presented to the DSMB included information on accrual and retention, comparability of the CAB LA and TDF/FTC arms at enrollment, and adherence, AEs and HIV-1 incidence by arm.

The trial was intended to continue until 114 events or a stopping boundary was crossed. The DSMB used an O'Brien-Fleming boundary to consider stopping the trial early for efficacy. On November 5, 2020, the National Institute of Allergy and Infectious Diseases DSMB agreed that the primary question of whether CAB LA prevents HIV-1 infection had been answered in the affirmative and was highly statistically significant. Because of these results, the DSMB recommended that the blinded portion of the study be stopped and that no further enrollment occur under Protocol Version 2.0. At this time, participants were to be unblinded to their study allocation. Consistent with the DSMB recommendation and procedures implemented for the related HPTN 083 trial, participants were allowed to continue the active study drug to which they had been assigned (without accompanying placebo) until further notice. In addition, the protocol team has developed a protocol amendment to offer participants in the TDF/FTC group open-label CAB. At the time of this early termination, a total of 3,224 participants had been enrolled into the study.

Endpoint Adjudication Committee

All reactive/positive HIV-1 test results were reviewed by an independent HIV Endpoint Adjudication Committee whose responsibility was to determine whether the test results met the primary endpoint of the study of HIV-1 infection.

Sample Size Considerations

Sample Size Assumptions

The primary analysis was based on HIV-1 incidence during Steps 1 and 2. It was assumed that participants would be followed between 81 (latest enrollees) and 185 (earliest enrollees) weeks in Steps 1 and 2 (1.6-3.6 years), with a uniform distribution of enrollments over a two-year period. Thus, the average time in Steps 1 and 2 was anticipated at 133 weeks (2.6 years). Sample size calculations were based on the following assumptions:

- Background HIV-1 incidence, in the absence of any PrEP, of 3.5% per year
- Both CAB LA and TDF/FTC are 85% effective when used with 100% adherence
- 2.5% one-sided type I error rate and 90% power at the indicated alternative
- Average follow-up duration of 2.6 years (range: 1.6-3.6 years)
- Maximum 5% lost-to-follow-up per year

Table 73 presents five scenarios (all superiority designs) and associated total sample sizes. The first scenario assumed that adherence to TDF/FTC and CAB/CAB LA was 50% and 85%, respectively, averaged over the entire Step 1 and 2 follow-up period. The second and third scenarios assumed a higher adherence to TDF/FTC (second line) and lower adherence to CAB LA (80%) (third line) (these scenarios were considered unlikely). The last 2 scenarios retained the conservative assumption of 80% adherence to CAB LA and assumed lower adherence to TDF/FTC of 45% and 48%. The largest blinded trials of TDF/FTC among women in a similar setting have shown even lower adherence than that assumed in Table 73 (see Section 7.8.4.1 of the study protocol). Given this history, a sample size of at least 3,128 was planned (111 events for a fixed sample size trial; 114 events to allow for interim monitoring) to provide an adequate degree of robustness against uncertainties in adherence rates to the two drug regimens.

Table 73. Table of 5 Case Scenarios, Trial HPTN 084

Adherence		HIV-1 Incidence (%/Year)[1]				
TDF/FTC	CAB LA	TDF/FTC	CAB LA	RR	# Events	Sample Size
0.50	0.85	2.01	0.97	0.48	78	2,352
0.55	0.85	1.86	0.97	0.52	98	3,112
0.50	0.80	2.01	1.12	0.56	125	3,590
0.48	0.80	2.07	1.12	0.54	111	3,128
0.45	0.80	2.16	1.12	0.52	98	2,686

Source: Applicant table.
[1] Background incidence is reduced by a weighted average of fully adherent and nonadherent individuals e.g., 2.01=3.5*((1-.85)*.5+1*(1-.5))
Abbreviations: CAB LA, long-acting cabotegravir; RR, risk ratio; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Rationale for NI Margin

An NI margin is typically chosen to preserve (at least) p% of the proven benefit of the active control (TDF/FTC in this case). Such a margin may be defined as (1-p)*log(RRL) where RRL is the lower bound of the 95% CI of the risk ratio (RR, placebo versus PrEP). Typically, NI trials are designed to preserve at least 50% of the benefit of the active control giving a margin that is halfway (on a log scale) between RRL and 1.0.

A critical issue in the design of NI trials is the assumption of constancy, namely, that the key conditions that lead to efficacy of the active control versus placebo in previous trials also hold in the current NI trial. In the context of a PrEP trial with TDF/FTC as the active control the most important constancy assumption is that adherence to TDF/FTC is comparable to previous trials where TDF/FTC has proven effective. This suggests that the NI margin of a PrEP trial with TDF/FTC as the active control should be based on the observed adherence in the current trial – if observed adherence is low then an NI margin of 1.0 (superiority) is required; if observed adherence is high, then an appropriate NI margin may be chosen based on the metaregression model (1) described above.

An NI trial uses the following hypotheses:

Ho: RR = margin

Ha: RR < margin

Table 74 gives, for CAB LA adherence of 85% and various levels of TDF/FTC adherence, the NI margin that preserves at least 50% of the active control benefit based on the metaregression shown in Figure 7.1 in the protocol, as well as the expected RR under the alternative hypothesis, number of events needed for 90% power, and sample size. Other assumptions are as noted previously.

Based on this table an analysis with a variable, adherence-dependent margin that preserves at least 50% of the proven benefit of TDF/FTC is well-powered for TDF/FTC adherence from 55% up to 64%, assuming the sample size of 3,200.

Table 74. Table of Noninferiority Designs for Various Levels of TDF/FTC Adherence Using a Margin Based on Figure 7.1 in the Study Protocol

TDF/FTC Adherence (%)	RR (CAB Vs. TDF)	Margin	No. HIV-1 Events for 90% Power	N Total	Maximum Observed RR[1]
55	0.52	1.12	71	2,254	0.70
60	0.56	1.17	77	2,572	0.75
65	0.62	1.22	92	3,256	0.81
70	0.68	1.27	108	4,062	0.87

Source: Applicant table.
[1] Maximum observed RR which would give a noninferiority result for this margin and this number of events.
CAB adherence assumed to be 85%; other assumptions are the same as in table in Sample Size Considerations section.
Abbreviations: CAB, cabotegravir; RR, risk ratio; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Response Rate Assumptions

Not applicable.

Analysis Population and Timepoint Description

Table 75. Analysis Population and Timepoint Description, Trial HPTN 084

Population	Definition / Criteria
Randomized population	• All participants who were randomized.
ITT (intent-to-treat)	• All participants who were randomized, excluding those who were inappropriately enrolled.
mITT (modified intent-to-treat)	• The ITT population, excluding those who were found to be HIV-1 infected at randomization.
PP (per protocol)	• The mITT population excluding all participants with protocol violations that were judged to be exclusionary from the per-protocol population.
Injection (Step 2) efficacy population	The mITT population who received at least 1 injection and were uninfected at the time of the first injection. Analysis period: Follow-up time will include primary analysis study time from the time of the first injection through the completion of the blinded injection phase of study follow-up.
Safety	• All ITT participants who received at least 1 dose of oral or injectable product.
Injection (Step 2) safety population	• All safety population participants who received at least 1 injection during Step 2.
Longitudinal PK CAB concentration population	A longitudinal evaluation of CAB PK in the CAB arm was conducted in 150 participants who received all injections up through Week 57, selected with the following regional distribution • 40% cisgender women <25 years of age at enrolment • 40% cisgender women between 25 and 30 years of age at enrolment • 20% cisgender women ³30 years of age at enrollment This population was used for the CAB concentration listing and to enhance the population represented in the global modelling of CAB-LA PK.
TDF/FTC adherence population	• Cohort of approximately 400 participants randomly selected at Baseline from the oral TDF/FTC arm.
Pregnancy population	• All participants who had a positive pregnancy test result while on treatment
Confirmed pregnancy population	• All participants who had a positive pregnancy test result while on treatment that was followed by a positive confirmatory test result at least 4 weeks later or confirmation by another method (e.g., ultrasound, full- or preterm live birth or investigator assessment consistent with active pregnancy).
Seroconverters	• *Primary seroconverter population* - All ITT participants who were HIV-1-uninfected at randomization and acquired HIV-1 infection during the primary analysis follow-up. • *Infected at enrollment seroconverter population* - All ITT participants who were determined to be HIV-infected at randomization.

Source: Applicant table.

Important participant subgroups were:

- Age: <25 versus ≥25 years old
- BMI < and ≥30 mg/m^2

Analysis Description

Primary Efficacy Analysis Description

mITT: An mITT analysis was used as the primary assessment for the efficacy comparison. Thus, any participant determined to be HIV-1 infected prior to randomization was omitted from the analysis. The HIV-1 incidence rate was calculated as the total number of participants with confirmed incident HIV-1 infection during study follow-up of Step 1 and Step 2 (through the termination of the blinded portion of the trial) divided by the PY accumulated in each arm. 95% CIs were calculated.

Cumulative incidence over follow-up for each arm was computed using product limit estimates and plotted with 95% CIs.

Treatment efficacy was estimated as treatment effect (TE)=1-HR. The HR comparing CAB LA versus TDF/FTC and 95% CIs was estimated using a Cox proportional hazards model with treatment arm as the only covariate, stratified by site using data from Steps 1 and 2 only, cutting the data at the time the blinded portion of the trial was stopped. The hypothesis Ho: HR=1.0 versus Ha: HR≠1.0 using α =0.05 was tested. If the number of events was small (<40) then the p-value was confirmed using a permutation test based on 100,000 random permutations of the treatment assignments; if there was a meaningful difference between the permutation and asymptotic procedures, the permutation p-value was used.

OBSP: A secondary on blinded study product analysis was conducted. The methods for this analysis were identical to the methods used for the primary analysis but participants were censored when an injection was first delayed. Specifically, follow-up time for a participant was censored at the last HIV-1 test that was within 10 weeks of the last nondelayed injection (6 weeks if the last nondelayed injection was the Week 5 injection). The last nondelayed injection was defined as the earliest injection whose subsequent injection is delayed (i.e., given >6 weeks after the Week 5 injection or >10 weeks after any other injection) or the last injection before a termination or a permanent product discontinuation.

Sensitivity and Supportive Statistical Analyses Description

Primary Safety Analysis

The primary prespecified safety comparison between arms was based on all AEs with maximum Grade ≥2. The reporting of safety data was descriptive and included all participants who received at least one dose of the investigational product.

AEs and SAEs: AEs were summarized using MedDRA (Version 23.1) system organ class and PTs. Tables show by treatment arm the number and percentage of participants experiencing an AE within a system organ class and within PT category by severity (grade). For the calculations in these tables, a participant with multiple AEs within a PT category was counted once under the maximum severity. Formal statistical testing comparing arms was not planned since interpretation of differences must rely heavily upon clinical judgment. A listing of SAEs reported to the DAIDS RSC safety office provided details of the events including severity, time between onset and last dosing, and cumulative number of doses received. SAE case narratives were from GlaxoSmithKline/ViiV and were based on SAE source information provided by RSC and reconciliation of certain fields within the clinical study database.

SAEs provided to GSK via the RSC included SAEs occurring during pregnancy as well as pregnancy outcomes fulfilling serious criteria. Nonserious AEs of exposure during pregnancy and live births were also provided to GSK by the RSC. Infants experiencing SAEs had infant-specific SAE forms in the GSK safety database, provided by the RSC. Nonserious AEs occurring during pregnancy and pregnancy outcomes which did not fulfil serious criteria were reported to the clinical database.

Local laboratory values: The actual value and change from baseline was summarized for each clinical chemistry, hematology, lipid panel, and urinalysis parameters and by each visit. In the event of repeat values, the last nonmissing value per visit was used. Values outside of the lab parameter's normal range was flagged as high, low, or abnormal based on the range of the test. Laboratory results were summarized by scheduled study visit. Summary calculations such as maximum postbaseline level included data from interim (unscheduled) visits. Any assessments that occurred while participants were on open-label TDF/FTC were excluded. Formal comparisons of laboratory findings between arms were not done.

Adverse Events in Step 1 OBSP

Objective: To compare the safety of oral CAB versus oral TDF/FTC in Step 1

Population: Primary safety

Censoring: AEs were censored at 120 days after randomization for participants who never received an injection; at the date of termination or investigational product discontinuation; at date of first injection; or at date of unblinding, whichever occurred first. Reported AEs were excluded if they occurred after the censoring time. Any AE that occurred while the participant was on open-label TDF/FTC was excluded.

Adverse Events in Step 2 OBSP

Objective: To compare the safety of CAB LA versus oral TDF/FTC proximal to blinded study drug administration

Population: Step 2 Safety

Censoring: AEs were censored at using OBSP censoring.

Study time was censored at 10 weeks after the time of the last blinded injection if beyond Week 5 or at 6 weeks if the last injection was Week 5, at date of unblinding, at ART start date, at date when Step 3 drug was dispensed, whichever occurred first. Reported AEs were excluded if they occurred before the first injection or while the participant was on open-label TDF/FTC.

Table 76. Summary of Study Phases (Steps) and Associated Analyses, Trial HPTN 084

Study Phase	Efficacy Analysis	Safety Analysis
Step 1 (blinded oral lead-in phase)	Efficacy analysis: Step 1 included time between randomization and the first injection date or study product discontinuation and/or study termination date, whichever occurred first.	Safety analysis: Step 1 included assessments on or after the date of enrollment up to the first injection, treatment discontinuation or study termination. Any assessments that occurred while the participant was on open-label TDF/FTC were excluded. On blinded study product safety analysis: Step 1 included AE(s) with onset date between the date of randomization and the first injection date, the date of study product discontinuation/study termination, date of unblinding, OR 120 days postrandomization (whichever occurred first). Any AE that occurred while the participant was on open-label TDF/FTC was excluded.
Step 2 (blinded injection phase)	Efficacy analysis: Step 2 included time from the first injection through the termination of the study. On blinded study product efficacy analysis: Step 2 included time from the first injection up to the first time the blinded injection was not given or delayed for any reason (refer to OBSP censoring explanation).	Safety analysis: Step 2 included assessments on or after the date of first injection through treatment discontinuation or study termination. Any assessments that occurred while the participant was on open-label TDF/FTC were excluded. On blinded study product safety analysis: Step 2 included AE(s) with onset date on or after the first injection through 6 weeks (if only 1 injection was given) or 10 weeks (if 2 or more injections were given) after the last blinded injection OR the first open-label pill dispensation on or after the first Step 3 Start Date (open-label TDF/FTC), OR date of unblinding, OR antiretroviral start date, whichever occurred first. Any AE(s) that occurred while the participant was on open-label

Study Phase	Efficacy Analysis	Safety Analysis
		TDF/FTC were not included in safety OBSP.
Open-label TDF/FTC (OLT) Step 3 Discontinued study product during Step 2 and entered open-label TDF/FTC for 48 weeks post last injection.	This data was included in the efficacy analyses but excluded from the OBSP efficacy analysis.	This data was considered part of the Tail Phase and throughout the study for safety analysis and was not included in Safety OBSP.
Protocol planned transition to Step 3: Completed Week 185 (last day of Step 2) and were offered open-label TDF/FTC for 48 weeks post last injection.	No participants had protocol planned transition to Step 3.	No participants had protocol planned transition to Step 3.
Tail Phase: Follow-up time through 48 weeks after Step 2 OBSP end date.	This data was included in efficacy analyses but excluded from the OBSP efficacy analysis.	The Tail Phase included AEs with onset date after the end date of Step 2 OBSP through 48 weeks of follow-up. Data after the participant returned to unblinded randomized treatment was not included.
Annual follow-up No study product or open-label product were administered. Annual follow-up visits for any participant who had not seroconverted, had discontinued treatment, or had completed 48 weeks of open-label TDF/FTC post last injection, and had not terminated the study.	This data was included in efficacy analyses but excluded from the OBSP efficacy analysis.	This data was included in the primary safety endpoint assessing AE(s) throughout the study and if data were within 48 weeks after Step 2 OBSP end date then that data was also included in Tail Phase.
Throughout the study	---	Step 1, 2, 3 and annual follow-up, used for the primary safety endpoint. All data regardless of treatment was included.

OBSP efficacy analysis censoring:

Censoring for the OBSP efficacy analysis excluded any time affected by delayed injections. Participants were censored the first time an injection was delayed, which was defined as follows:

For STEP 2:

1. Last nondelayed injection: The earliest of an injection whose subsequent injection was delayed for the first time (i.e., given >6 weeks after the Week 5 injection or >10 weeks after any other injection) or the last injection before a termination or a permanent product discontinuation.
2. For participants with a delayed injection, follow-up time was censored at the last visit with HIV-1 status determined up through 6 weeks after the Week 5 injection, if that was the last nondelayed injection, or 10 weeks after the last nondelayed injection for subsequent injections.
3. For participants with no delayed injections, analysis time was defined as for primary efficacy analysis.

Study Phase	Efficacy Analysis	Safety Analysis
OBSP Safety Analysis Censoring: For STEP 1: For a participant who never received an injection, AEs were censored when the onset date fell after the earliest of 120 days after randomization, date of unblinding, or at the termination or permanent product discontinuation date. This included AEs reported for participants who did not receive any injectable product. The earlier date of Date of First Injection - 1, Step 1 Start Date +120, date of unblinding, date of treatment discontinuation, or date of study termination was used. For STEP 2: For participants who received an injection, AE follow-up was censored after the last injection regardless of any delays in injections. If only one injection was given, the participant's safety events were censored at 6 weeks after the first injection, or 10 weeks after the last injection if more than one injection was given, or the first open-label pill dispensation on or after the first Step 3 Start Date (Open-label TDF/FTC), OR date of unblinding, OR antiretroviral start date, whichever occurred first.		

Source: Applicant table. Copyright 2021 the ViiV Healthcare group of companies. All rights reserved. Unauthorized copying or use of this information is prohibited.
Abbreviations: AE, adverse event; OBSP, on blinded study product; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Measurement of Adherence (TDF/FTC)

TDF/FTC adherence was measured at a subset of study visits in a random sample of participants enrolled into Arm B (active TDF/FTC). Four hundred participants were targeted for this analysis. A participant was defined as adherent at a given visit if her plasma TFV level was greater than 0.31 ng/mL, a concentration which is associated with any detectable plasma TFV. See study protocol Section 7.8.4.2 for more details.

Analyses of Secondary Objectives

- To compare HIV-1 incidence among participants receiving oral CAB/CAB LA versus daily oral TDF/FTC (Steps 1, 2 and 3)

The HR comparing CAB LA versus TDF/FTC and a 95% CIs were estimated using a Cox proportional hazards model with treatment arm as the only covariate, stratified by site and using all HIV-1 incidence data from steps 1 through 3. The hypothesis Ho: HR =1.0 versus Ha: HR <1.0 using α=0.025 was tested.

- To evaluate relative efficacy of oral CAB/CAB LA versus oral TDF/FTC in subgroups defined by the baseline factors of: age, HSV-2 serostatus, contraceptive method, and BMI.

For each of the specified baseline factors, a Cox proportional hazards model was fitted with treatment arm, baseline factor, and their interaction as covariates, stratified by site. For baseline factor x, the model may be written as:

$$\log(\lambda(t; arm, x, s)) = \log(\lambda_s(t)) + \beta_1\, arm + \beta_2 x + \beta_3 arm * x$$

The HR for the baseline factor equal to each level of x was estimated as $\exp(\beta_1+\beta_3\, x)$ and the corresponding treatment efficacy was estimated as TE =1-HR. 95% CIs for the HR for each level

of x were reported. The clinical significance of differences in the estimated efficacy between subgroups were evaluated. If relevant, a test for effect modification was conducted based on the hypotheses Ho: $\beta 3=0$ versus Ha: $\beta 3 \neq 0$.

- To describe and model the relationship between HIV-1 incidence and drug concentration levels, within each arm.

A Cox proportional hazards model with drug concentration as a continuous, time-dependent covariate was fitted separately for each arm, with stratification by site. Martingale residual plots were used to guide selection of an appropriate functional form for drug concentration, starting with the assumption of a linear relationship between drug concentration and log hazard. Separate models were fitted for different measures of drug levels (i.e., DBS, plasma). The team also investigated using a model to predict drug concentrations in continuous time based on observed plasma and DBS drug levels; the predicted values could then be used as a covariate in the analysis proposed here. Potential confounders (e.g., age, sexual risk behaviors) were included in the model. Once a final model was selected, the (possibly adjusted) relationship between log relative risk (y-axis) and drug concentration (x-axis), with 95% confidence intervals, was plotted for each arm. We note that since this was an observational analysis (i.e., individuals were not randomized to drug levels), all inferences were associative, not causal.

- To describe the distribution and correlates of drug concentration levels, within each arm.

Boxplots of drug concentration over follow-up overall and by age groups (≤ 24 versus >24), separately for each arm were plotted.

A mixed effects linear regression model with log of drug concentration as the outcome, a random effect for participant, and potential correlates of drug concentration as covariates were fitted to the longitudinal drug concentrations. Separate models were fitted for each arm. The association between drug concentration and each potential correlate was evaluated by testing the corresponding regression coefficient using the hypotheses, Ho: $\beta=0$ versus Ha: $\beta \neq 0$ with $\alpha=0.05$.

- To compare the acceptability of and preferences for CAB LA versus oral TDF/FTC.

Descriptive statistics were used to summarize acceptability measures as evaluated at the end of the study. The specific statistics chosen depended on the form of the acceptability assessment.

Qualitative Analysis

All semistructured interviews and observations were conducted by trained, same-sex interviewers, audio-recorded, transcribed and translated into English, and then uploaded into a qualitative software analysis program (such as NVivo 12). A team representing core and site behavioral investigators followed a process of reading, coding, data display and data reduction in order to explore in greater depth participants' attitudes towards and experiences with the product they were assigned. Detailed memos and/or matrices were developed to examine how participants' perceptions related to product use (i.e., ease of use, perceived efficacy, side effects) and to trial participation (i.e., motivations for participation, interactions with trial staff, impact on partner or other social relationships), influence acceptability, and interest in future use of an injectable PrEP product.

- To estimate sexual risk behaviors, as measured by self-report and rates of incident STIs.

Key sexual behaviors (numbers of partners, unprotected sex) were dichotomized (i.e., >1 partner, any unprotected sex). All postrandomization visits where the outcome information was collected were included in the analysis. Mixed effects logistic regression was used to estimate prevalence and 95% CIs for each behavior. All analyses used a robust variance. Results were reported overall and by arm.

Rates of incident STIs were computed for each arm as number of new STIs divided by total PY. Poisson regression with a robust variance was used to model the number of incident STIs for each woman. Person-time was used as an offset. Incidence and a 95% CI were reported overall and by arm.

- To compare Grade >2 AE rates in women with baseline BMI </≥25 kg/m^2, within each study arm

Local reactions, AEs and local laboratory values were summarized as described separately for women with baseline BMI </≥25 kg/m^2.

A multiplicative intensity model was used to compare rates of Grade 2 or higher AEs between women with BMI >25 kg/m^2 versus <25 kg/m^2, with separate models for each arm. The model included time to Grade 2 or higher AEs for each participant as the outcome and BMI category as a covariate. The coefficient of BMI category was used to compare AE rates based on the hypotheses, Ho: $\beta_{bmi}=0$ versus Ha: $\beta_{bmi} \neq 0$ with $\alpha=0.05$. AEs were clustered by participant and a robust variance was used.

- To compare differences in weight gain and BMI, by arm

Weight gain was computed as change from baseline (enrollment) at each follow-up visit. Mean weight gain over follow-up by (time-varying) current treatment (i.e., as-treated analysis) was plotted. A linear mixed model was fitted with categorical intervals for time in study, (time-varying) treatment and time by treatment interaction to evaluate the effect of CAB LA on weight gain.

- To compare pregnancy incidence and outcomes between arms

To compare pregnancy incidence between the arms, a Poisson regression with number of pregnancies for each participant as the outcome, follow-up time as an offset and arm as the covariate was fitted. Robust variances were computed and the coefficient of arm was evaluated using the hypotheses, Ho: $\beta_{arm}=0$ versus Ha: $\beta_{arm} \neq 0$ with $\alpha=0.05$.

A table describing pregnancy outcomes for each arm was provided.

- To evaluate rates of HIV-1 drug resistance among participants who acquire HIV-1 infection during the study among participants receiving oral CAB/CAB LA versus oral TDF/FTC

The number, proportion, and types of resistance mutations were reported by arm for all postrandomization HIV-1 seroconverters, separately for each step of the trial. No formal statistical test was performed.

- To determine plasma concentrations of DMPA or NET-EN or etonogestrel when co-administered for contraception with study products (TDF/FTC or CAB LA)

For each contraceptive subgroup (DMPA,NET-EN, etonogestrel), the proportion of women in the CAB LA arm with contraceptive drug levels (DMPA, NET-EN, etonogestrel for the three contraceptive subgroups, respectively) below the contraceptive threshold (0.1 ng/mL for DMPA, TBD for NET-EN and 90 pg/mL for etonogestrel) was estimated. The 95% CIs for the proportion were provided. The CI was based on a robust variance if multiple observations were available for each woman.

In addition, mean contraceptive drug concentrations (and/or other PK parameters) between the CAB LA and TDF/FTC arms for each contraceptive subgroup using a t-test (or a t-test with robust variance if multiple observations on each woman are available) were compared.

Analyses of Exploratory Objectives

- To compare the estimated programmatic cost, cost-effectiveness, and disease impact indicators of CAB LA versus daily oral TDF/FTC versus no PrEP for HIV-uninfected women in the study sites locations.
- To perform secondary laboratory assessments that may include evaluation of factors related to HIV-1 infection, hepatitis infection, and other infections; ARV drug use; pharmacogenomics; characterization of HIV-1 in infected participants; and evaluation of laboratory assays related to the study objectives.

Analysis plans for the assessments described in the laboratory exploratory objective will be determined at a later date based on the specific types of testing/assessments performed.

Changes in Conduct of the Study or Planned Analyses

Early Termination

The independent DSMB recommended early termination of the blinded, randomized portion of the study on November 5, 2020, after an interim analysis indicated that the prespecified stopping criteria for superiority was met. Results indicated that a PrEP regimen containing CAB LA injected once every 8 weeks was superior to daily oral TDF/FTC for HIV-1 prevention among women. The DSMB recommended the blinded, randomized portion of the study be stopped early and results released. The data summarized for this study for this report include the blinded portion of the study only (all data up until November 5, 2020).

SAP Modifications

The SAP was amended while the blinded statistician was still blinded to individual participant randomized treatment as follows:

COVID Disruption

In June 2020, the SAP was modified to allow the protocol team to administratively censor a period of follow-up data from any study site that was “significantly disrupted” by the COVID pandemic. Specifically, if retention at a site fell below a predetermined metric, all follow-up data

from that site for the disrupted period would be excluded from the primary analysis. This procedure was documented in the SAP v2.0. The protocol team reviewed disruption data in July and October 2020 and determined that no sites were significantly disrupted, and no periods would be excluded from the analysis for any sites.

Analysis Populations

- Populations were adjusted, renamed, or clarified: mITT; per protocol; seroconverter; contraceptive substudy; pregnancy.
- Populations were added: Randomized; intent-to-treat; primary safety; Step 2 safety; Step 2 efficacy; longitudinal pharmacokinetic CAB; TDF/FTC adherence population; confirmed pregnancy; seroconverter population; primary seroconverters; declined contraception; infected at enrollment
- The SAP version 2.0 "per protocol" analysis dataset was redefined and renamed as OBSP censoring. The new "per protocol" population was defined as being based upon deviation adjudication. The adjudication process was described.
- The age and BMI subgroups were modified with adjusted cut-points.

Analysis Details and Clarifications

Clarifications and additional details were added throughout the Statistical Analysis section.

- A section was added to describe missing data handling and imputations.
- Appendices were added to provide detail for visit windowing, efficacy and safety analysis censoring details and OBSP specifications, a listing of study sites, a listing of AEs of special interest (AESIs). Key variable definitions, which were based on data fields found in the case report form data, were removed.

The efficacy analyses that included Step 3 were excluded due to the timing of the blinded portion of the study stopping early. At that time, no participants had entered into the protocol-defined Step 3 and therefore, the efficacy analyses that included Step 3 were no longer informative. Therefore, the following endpoints were not performed for this CSR:

- Number of documented incident HIV-1 infections in Steps 1, 2, and 3

The HSV-2 serostatus and contraceptive method subgroup efficacy analyses are outside the scope of this CSR and will be the subject of a separate reporting effort.

- Number of documented incident HIV-1 infections in participants in subgroups broken down by HSV-2 status and contraceptive use method.

The following tertiary endpoints will be explored later and were not included in this report:

- To compare Grade ≥2 AE rates in women with baseline BMI </≥25 kg/m^2, within each study arm.
- To determine plasma concentrations of DMPA, NET-EN or etonogestrel when co-administered for contraception with study products (TDF/FTC or CAB LA).

The following deviations from the SAP were performed after the blinded statistician had been unblinded.

- Participant who might be lost to follow-up was still being counted as ongoing unless the site entered a study termination reason as "Other" with a subreason of "Lost to Follow-up."
- Resistance data was summarized by treatment arm for all seroconverters, but they were not summarized by treatment arm for each step of the trial separately. This detail is provided in the listing.

Reports

- A new section was added to describe the contents of the following reports: Performance metrics, Study Monitoring Committee, DSMB, and CSR.

16. Efficacy: Additional Information and Assessment

16.1. Additional Analyses for HPTN 083

16.1.1. Additional Analyses for Subject Disposition and Baseline Demographic and Clinical Characteristics

This section supplements the analyses and interpretation presented in Section 6.2.1.4.

The treatment status at the cutoff date using the AE in the disposition dataset (ADDS) is shown below and is the same as Table 1 in the CSR. Approximately 79% of subjects in both arms had ongoing treatment. The 58 seroconversions listed in the table include 5 baseline seroconversions, 1 site positive that was not adjudicated as it became negative later, and 52 endpoints (adjudicated seroconversions).

Table 77. Patient Disposition of Treatment Status, Randomized Population, Trial HPTN 083

Randomized Treatment Status	CAB (N=2,283) n (%)	TDF/FTC (N=2,287) n (%)
Ongoing	1,814 (79.5)	1,794 (78.4)
Completed*	28 (1.2)	49 (2.1)
Completed due to seroconversion (based on site positive)	16	42
Completed Week 145 visit	12	7
Discontinuation from randomized treatment	406 (17.8)	401 (17.5)
Terminated from study without discontinuation from randomized treatment	35 (1.5)	43 (1.9)

Source: Statistical reviewer, ADDS and SAS software were used.
Abbreviations: CAB, cabotegravir; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Participants status by Step is listed in Table 78. Over 90% of subjects in both arms entered the injection phase (Step 2) and slightly over 10% of subjects in both arms entered Step 3 when the study was unblinded.

Table 78. Summary of Participants Status by Step, Randomized Population, Trial HPTN 083

Subject's Status by Step	CAB (N=2,283) n (%)	TDF/FTC (N=2,287) n (%)
Entered Step 1 (oral phase)	2,283 (100)	2,287 (100)
Still in Step 1 at cutoff date	11	8
Discontinued IP without termination of study during Step 1 (Entered annual follow-up during Step 1)	132	175
Terminated study during Step 1	23	23
Completed Step 1 and entered Step 2	2,117 (93)	2,081 (91)
Entered Step 2 (injection phase)	2,117 (93)	2,081 (91)
Still in Step 2 at cutoff date	1,803	1,786
Discontinued IP without termination of study during Step 2 (Entered Step 3 early)	276	255
Terminated study during Step 2	26	33
Completed Step 2 and entered Step 3	12	7
Entered Step 3 (at Week 153 or prior to Week 153)	288 (13)	262 (11)
Still in Step 3 at cutoff date	198	191
Completed Step 3 (who have been followed for 48 weeks)	82	58
Terminated study during Step 3	8	13

Source: Statistical reviewer, ADDS and SAS software were used.
Abbreviations: CAB, cabotegravir; IP, investigational product; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 79 listed additional baseline demographic and clinical characteristics.

Table 79. Some Additional Baseline Demographic and Clinical Characteristics, mITT Population, Trial HPTN 083

Characteristics	CAB	TDF/FTC	Total
mITT population			
n	2,280	2,281	4,561
Number of sexual partner at baseline			
n	2,073	2,046	4,119
Mean (SD)	4.7 (8.1)	5.0 (9.3)	4.9 (8.7)
Median (Q1, Q3)	3 (2, 3)	3 (2, 3)	3 (2, 5)
(Min, Max)	(0, 200)	(0, 200)	(0, 200)
Number of condomless receptive anal sex at baseline			
n	1,379	1,329	2,708
Mean (SD)	2.5 (4.4)	2.7 (6.0)	2.6 (5.2)
Median (Q1, Q3)	1 (0, 3)	1 (0, 3)	1 (0, 3)
(Min, Max)	(0, 87)	(0, 149)	(0, 149)
Marriage status			
Have primary or main partner, not living together	171 (7.5%)	164 (7.2%)	335 (7.3%)
Living with primary or main partner	138 (6.1%)	154 (6.8%)	292 (6.4%)
Married/civil union/legal partnership	79 (3.5%)	98 (4.3%)	177 (3.9%)
Single/divorced/widowed	1,886 (82.7%)	1,860 (81.5%)	3,746 (82.1%)
Other	6 (0.3%)	5 (0.2%)	11 (0.2%)

Characteristics	CAB	TDF/FTC	Total
Education level			
College/University or higher, complete	867 (38.0%)	813 (35.6%)	1,680 (36.8%)
College/University or higher, not complete	707 (31.0%)	711 (31.2%)	1,418 (31.1%)
No schooling	2 (0.1%)	6 (0.3%)	8 (0.2%)
Primary school, complete	16 (0.7%)	25 (1.1%)	41 (0.9%)
Primary school, not complete	12 (0.5%)	17 (0.7%)	29 (0.6%)
Secondary school, complete	371 (16.3%)	409 (17.9%)	780 (17.1%)
Secondary school, not complete	119 (5.2%)	113 (5.0%)	232 (5.1%)
Technical training, complete	112 (4.9%)	108 (4.7%)	220 (4.8%)
Technical training, not complete	74 (3.2%)	79 (3.5%)	153 (3.4%)
Job status			
Full-time employm	1,154 (50.6%)	1,174 (51.5%)	2,328 (51.0%)
Not employed	600 (26.3%)	619 (27.1%)	1,219 (26.7%)
Part-time employm	526 (23.1%)	488 (21.4%)	1,014 (22.2%)
Weight (kg) at baseline			
n	2,277	2,279	4,556
Mean (SD)	76.7 (19.1)	76.7 (19.0)	76.7 (19.0)
Median (Q1, Q3)	73.4 (64.0, 85.3)	73.0 (63.6, 85.0)	73.2 (63.8, 85.1)
(Min, Max)	(41.0, 189.0)	(39.70, 219.0)	(39.70, 219.0)
Height at baseline			
n	2,277	2,279	4,556
Mean (SD)	173.1 (8.1)	173.5 (7.8)	173.3 (8.0)
Median (Q1, Q3)	173.0 (168.0, 178.6)	173.0 (168.0, 179.0)	173.0 (168.0, 179.0)
(Min, Max)	(109.7, 205.7)	(146.0, 201.0)	(109.7, 205.7)
BMI at baseline			
n	2,274	2,277	4,551
Mean (SD)	25.48 (5.597)	25.36 (5.346)	25.42 (5.473)
Median (Q1, Q3)	24.4 (21.8, 27.9)	24.5 (21.7, 27.7)	24.5 (21.8, 27.8)
(Min, Max)	(14.7, 91.0)	(14.3, 67.4)	(14.3, 91.0)
Site			
700	14 (0.6%)	12 (0.5%)	26 (0.6%)
701	32 (1.4%)	33 (1.4%)	65 (1.4%)
706	34 (1.5%)	34 (1.5%)	68 (1.5%)
709	17 (0.7%)	18 (0.8%)	35 (0.8%)
712	32 (1.4%)	33 (1.4%)	65 (1.4%)
714	89 (3.9%)	87 (3.8%)	176 (3.9%)
715	74 (3.2%)	75 (3.3%)	149 (3.3%)
721	119 (5.2%)	121 (5.3%)	240 (5.3%)
722	106 (4.6%)	109 (4.8%)	215 (4.7%)
732	89 (3.9%)	88 (3.9%)	177 (3.9%)
734	33 (1.4%)	33 (1.4%)	66 (1.4%)
745	29 (1.3%)	29 (1.3%)	58 (1.3%)
764	14 (0.6%)	12 (0.5%)	26 (0.6%)
780	36 (1.6%)	37 (1.6%)	73 (1.6%)
787	43 (1.9%)	43 (1.9%)	86 (1.9%)
791	69 (3.0%)	71 (3.1%)	140 (3.1%)
800	35 (1.5%)	35 (1.5%)	70 (1.5%)
801	30 (1.3%)	31 (1.4%)	61 (1.3%)
813	101 (4.4%)	102 (4.5%)	203 (4.5%)
816	78 (3.4%)	74 (3.2%)	152 (3.3%)
819	42 (1.8%)	39 (1.7%)	81 (1.8%)
820	33 (1.4%)	33 (1.4%)	66 (1.4%)
821	30 (1.3%)	32 (1.4%)	62 (1.4%)

Characteristics	CAB	TDF/FTC	Total
825	33 (1.4%)	34 (1.5%)	67 (1.5%)
831	87 (3.8%)	89 (3.9%)	176 (3.9%)
844	35 (1.5%)	34 (1.5%)	69 (1.5%)
845	77 (3.4%)	78 (3.4%)	155 (3.4%)
846	32 (1.4%)	31 (1.4%)	63 (1.4%)
847	40 (1.8%)	39 (1.7%)	79 (1.7%)
848	76 (3.3%)	74 (3.2%)	150 (3.3%)
850	100 (4.4%)	99 (4.3%)	199 (4.4%)
851	29 (1.3%)	29 (1.3%)	58 (1.3%)

Source: Statistical reviewer, ADSL and SAS software were used.
Abbreviations: CAB, cabotegravir; mITT, modified intention-to-treat; N, number of participants in treatment group; n, number of participants with given characteristic; SD, standard deviation; SE, standard error; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

16.1.2. Sensitivity Analyses of the Primary Efficacy Endpoint

The primary efficacy endpoint results were consistent across sensitivity analyses presented below.

The first sensitivity analysis used the injection Step 2 efficacy population for the primary endpoint analysis, which includes mITT population subjects who received at least one injection, were not infected at the time of the first injection (Step 1 infections were excluded) and had at least one follow-up visit with nonmissing HIV-1 test results after the first injection. The follow-up time started from beginning of injection. As a result, the number of subjects, number of infections, and PY of follow-up in both arms decreased (see Table 80).

The HR estimate was 0.21 with 95% CI (0.10, 0.45), and the seroconversion rate reduction estimate was 79% with 95% CI (55%, 90%), which confirmed Table 12 in the CSR.

Table 80. HIV-1 Seroconversion Rates and Hazard Ratio, Step 1 and 2, Injection Step 2 Efficacy Population, Trial HPTN 083

Parameter	CAB (N=2,109)	TDF/FTC (N=2,069)	Results
Number of HIV-1 infected events	8	37	
PY of follow-up	2,923	2,877	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.27 (0.12, 0.54)	1.29 (0.91, 1.77)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.210 (0.10, 0.45)
Superiority test p-value			<0.0001
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			79 (55, 90)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

The second sensitivity analysis used the OBSP population for the primary endpoint analysis, which includes injection Step 2 efficacy population subjects. The follow-up time was counted while subjects were compliant to the injection schedule and was censored at the first time of a delayed/missed injection. As a result, the number of infections, and PY of follow-up in both arms decreased compared to primary efficacy analysis results (see Table 81).

The HR estimate was 0.17 with 95% CI (0.06, 0.48), and the seroconversion rate reduction estimate was 83% with 95% CI (52%, 94%), which slightly differ from Table 11 in the CSR.

Table 81. HIV-1 Seroconversion Rates and Hazard Ratio, Step 1 and 2, On Blinded Study Product (OBSP) Population, Trial HPTN 083

Parameter	CAB (N=2,109)	TDF/FTC (N=2,069)	Results
Number of HIV-1 infected events	4	24	
PY of follow-up	2,459	2,445	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.16 (0.04, 0.42)	0.98 (0.63, 1.46)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.166 (0.06, 0.48)
Superiority test p-value			0.0009
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			83 (52, 94)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

In the third sensitivity analysis, the follow-up times for infected subjects were calculated as the number of days between enrollment and the first positive HIV-1 test results as determined by the Endpoint Adjudication Committee (EAC), instead of the number of days between enrollment and the midpoint between the last HIV-negative visit and first HIV-1 positive visit, as determined by the EAC. As a result, the number of PY of follow-up in both arms increased by approximately 3 years for both arms (see Table 82).

The HR estimate was 0.33 with 95% CI (0.18, 0.62), and the seroconversion rate reduction estimate was 67% with 95% CI (38%, 82%), which are almost identical to the primary efficacy analysis results.

Table 82. HIV-1 Seroconversion Rates and Hazard Ratio for Step 1 and 2 Using the First Positive HIV-1 Test Date as the End of Follow-Up Time, mITT Population, Trial HPTN 083

Parameter	CAB (N=2,280)	TDF/FTC (N=2,281)	Results
Number of HIV-1 infected events	13	39	
PY of follow-up	3,214	3,196	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.40 (0.22, 0.69)	1.22 (0.87, 1.67)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.329 (0.18, 0.62)
Superiority test p-value			0.0005
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			67 (38, 82)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Additional Baseline Infections Identified After the Primary Efficacy Analysis

In the supplemental folder of this NDA submission, the Applicant submitted four ADaM datasets, including ADSL, ASDTS, ADTTE, and ADPF, along with the supplemental virology report of HPTN 083. There were two additional subjects (Subject 300083-(b) (6) and Subject 300083(b) (6)), who were in the original mITT population and identified retrospectively as baseline infections.

- Subject 300083-[redacted] (b) (6) was in the CAB arm and was uninfected in the original mITT population.
- Subject 300083-[redacted] (b) (6) was in the CAB arm and was identified as infected at Day 74 in the original mITT population.

The updated primary endpoint analysis results excluding these two subjects from the original mITT population (referred to as the updated mITT) are listed below. The results were similar to the primary efficacy results with a slightly lower seroconversion rate in the CAB arm and a slightly lower HR. The raw HR was 0.30 with 95% CI (0.16, 0.58) and the seroconversion rate reduction estimate was 70% with 95% CI (42%, 84%). The bias-adjusted HR was 0.31 with 95% CI (0.16, 0.58).

Table 83. HIV-1 Seroconversion Rates and Hazard Ratio, Step 1 and 2, Updated mITT, Trial HPTN 083

Parameter	CAB (N=2,278)	TDF/FTC (N=2,281)	Result
Number of HIV-1 infected events	12	39	
PY of follow-up	3,211	3,193	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.37 (0.19, 0.65)	1.22 (0.87, 1.67)	
Cox regression results			
Hazard ratio (CAB vs. TFD/FTC) (95% CI)[2]			0.303 (0.16, 0.58)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			70 (42, 84)
Bias-adjusted results, corrected for early stopping[4]			
Hazard ratio - CAB vs TDF/FTC (95% CI)[2]			0.312 (0.16, 0.58)
Superiority - p-value			0.0003
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			69 (42, 84)

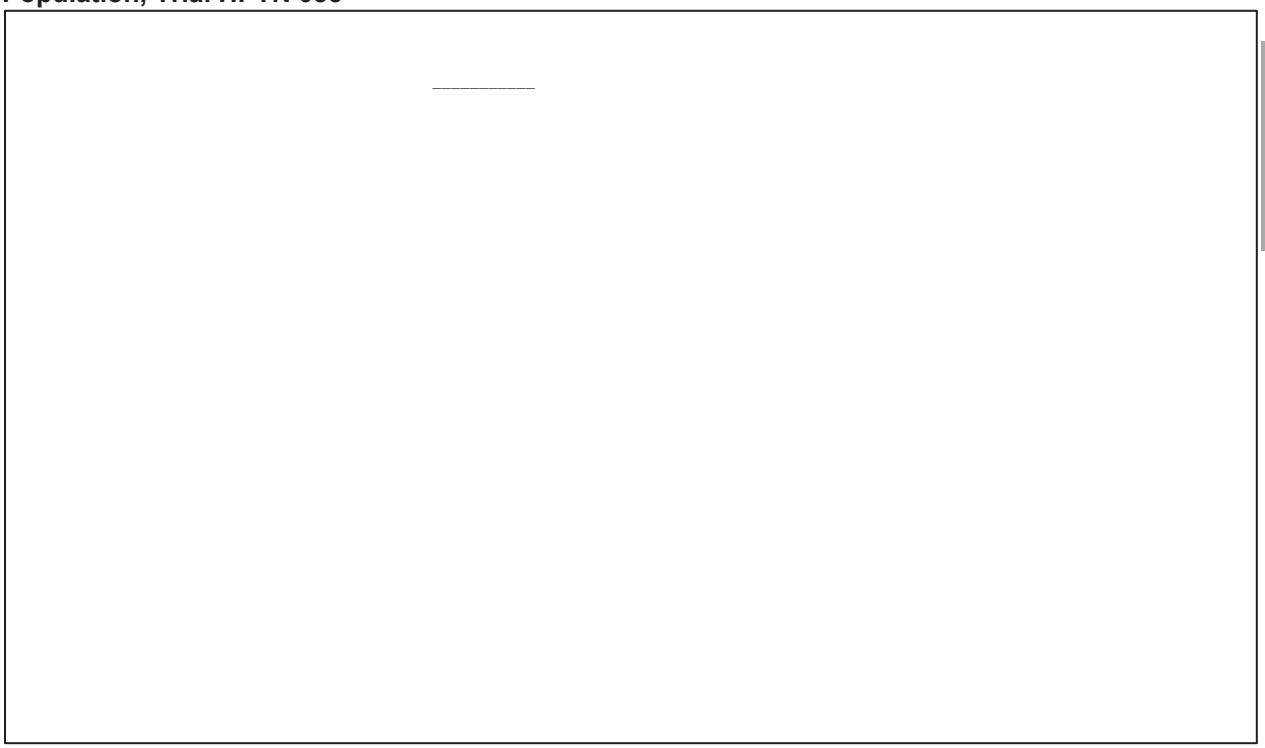
Source: Statistical reviewer, ADSL and ADTTE in the supplemental folder and SAS software were used.
[1] Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
[4] The bias-adjusted hazard ratio, CI and p-value account for the group-sequential trial design and the early stopping time with updated information fraction.
Abbreviations: CAB, cabotegravir; CI, confidence interval; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

16.1.3. Additional Subgroup Analyses for Primary Efficacy Endpoint

This section supplements the analyses and interpretation presented in Section 6.2.1.4. Of note, the sample sizes for many subgroups were small, which limits the ability to detect trends with certainty. Numerous subgroup analyses were conducted without any adjustment for the multiple analyses, which could result in spurious findings due to chance.

The subgroups analyzed were age groups, gender, race, ethnicity, region, and two other baseline factors. The results of subgroups analyzed here were similar to overall results (Figure 15).

Figure 15. Forest Plot of Subgroup Analyses Results of Primary Efficacy Endpoint, mITT Population, Trial HPTN 083



Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
Abbreviations: CI, confidence interval; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Subgroup Analyses by Age

The age subgroup was categorized as age <30 years and ≥30 years. The results from both age groups were very similar to the overall mITT results with a HR of 0.32, 95% CI (0.16, 0.63) and a risk reduction of 68% for <30 age group, and a HR of 0.39, 95% CI (0.08, 1.84) and a risk reduction of 61% for ≥30 age group.

Table 84. HIV-1 Seroconversion Rates in Age <30 Years, mITT Population, Trial HPTN 083

Parameter	CAB (N=1,570)	TDF/FTC (N=1,506)	Result
Number of HIV-1 infected events	11	33	
PY of follow-up	2,110	1,987	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.52 (0.26, 0.93)	1.66 (1.14, 2.33)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.32 (0.16, 0.63)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			68 (37, 84)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 85. HIV-1 Seroconversion Rates in Age ≥30 Years, mITT Population, Trial HPTN 083

Parameter	CAB (N=710)	TDF/FTC (N=775)	Result
Number of HIV-1 infected events	2	6	
PY of follow-up	1,101	1,206	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.18 (0.02, 0.66)	0.50 (0.18, 1.08)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.39 (0.08, 1.84)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			61 (-84, 92)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Subgroup Analyses by Cohort

There were two cohorts in the trial, MSM and TGW. Results from both cohorts were very similar to the overall mITT results. The 95% CI of the HR in the TGW cohort was wider than that in the overall mITT population and in the MSM cohort due to the smaller sample sizes.

Table 86. HIV-1 Seroconversion Rates in MSM Cohort, mITT Population, Trial HPTN 083

Parameter	CAB (N=2,011)	TDF/FTC (N=1,976)	Result
Number of HIV-1 infected events	11	32	
PY of follow-up	2,837	2,803	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.39 (0.19, 0.69)	1.14 (0.78, 1.62)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.35 (0.18, 0.68)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			75 (32, 82)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] 95% CI was calculated using the normal approximation of Poisson event variance.
[2] Hazard ratio and 95% CI were estimated based on a Cox proportional hazard model stratified by research center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CI, confidence interval; mITT, modified intention-to-treat; MSM, men having sex with men; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; TGW, transgender women

Table 87. HIV-1 Seroconversion Rates in TGW Cohort, mITT Population, Trial HPTN 083

Parameter	CAB (N=266)	TDF/FTC (N=304)	Result
Number of HIV-1 infected events	2	7	
PY of follow-up	371	389	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.54 (0.07, 1.95)	1.80 (0.72, 3.71)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.34 (0.08, 1.56)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			66 (-56, 92)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] 95% CI was calculated using the normal approximation of Poisson event variance.
[2] Hazard ratio and 95% CI were estimated based on a Cox proportional hazard model stratified by research center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CI, confidence interval; mITT, modified intention-to-treat; MSM, men having sex with men; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; TGW, transgender women

Subgroup Analyses by Race in the United States

This subgroup analysis only included participants from the United States who were grouped as Black and non-Black. Only 37% of all enrolled participants were from U.S. sites, and the sample sizes for this subgroup analysis were very small. Results from the Black subpopulation were

similar to the overall mITT results. The HR estimate for non-Black subgroup had a much wider 95% CI due to the smaller sample sizes.

Table 88. HIV-1 Seroconversion Rates in Black Subpopulation in the United States, mITT Population, Trial HPTN 083

Parameter	CAB (N=412)	TDF/FTC (N=427)	Result
Number of HIV-1 infected events	4	16	
PY of follow-up	691	703	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.58 (0.16, 1.48)	2.28 (1.30, 3.70)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.26 (0.09, 0.76)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			74 (24, 91)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] 95% CI was calculated using the normal approximation of Poisson event variance.
[2] Hazard ratio and 95% CI were estimated based on a Cox proportional hazard model stratified by research center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 89. HIV-1 Seroconversion Rates in Non-Black Subpopulation in the United States, mITT Population, Trial HPTN 083

Parameter	CAB (N=437)	TDF/FTC (N=421)	Result
Number of HIV-1 infected events	0	4	
PY of follow-up	836	801	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.00 (0.00, 0.44)	0.50 (0.14, 1.28)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.11 (0.00, 2.80)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			89 (-180, 100)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] 95% CI was calculated using the normal approximation of Poisson event variance.
[2] Hazard ratio and 95% CI were estimated based on a Cox proportional hazard model stratified by research center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Subgroup Analyses by Region

In the trial, geographic locations were classified into four regions, United States (37%), Latin America (43%), Asia (17%), and Africa (3%). Results from four regions were similar to the overall mITT results. The 95% CIs of HRs in four regions were wider than that in the overall mITT population due to the smaller sample sizes.

Table 90. HIV-1 Seroconversion Rates in the United States, mITT Population, Trial HPTN 083

Parameter	CAB (N=849)	TDF/FTC (N=848)	Result
Number of HIV-1 infected events	4	20	
PY of follow-up	1,528	1,504	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.26 (0.07, 0.67)	1.33 (0.81, 2.05)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.21 (0.07, 0.60)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			79 (40, 93)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] 95% CI was calculated using the normal approximation of Poisson event variance.
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by research center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 91. HIV-1 Seroconversion Rates in Latin America, mITT Population, Trial HPTN 083

Parameter	CAB (N=978)	TDF/FTC (N=982)	Result
Number of HIV-1 infected events	6	11	
PY of follow-up	1,021	1,011	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.59 (0.22, 1.28)	1.09 (0.54, 1.95)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.56 (0.21, 1.51)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			44 (-51, 79)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] 95% CI was calculated using the normal approximation of Poisson event variance.
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by research center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CI, confidence interval; mITT, modified intention-to-treat, PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 92. HIV-1 Seroconversion Rates in Asia, mITT Population, Trial HPTN 083

Parameter	CAB (N=375)	TDF/FTC (N=377)	Result
Number of HIV-1 infected events	2	6	
PY of follow-up	570	581	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.35 (0.04, 1.27)	1.03 (0.38, 2.25)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.39 (0.08, 1.82)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			61 (-82, 92)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] 95% CI was calculated using the normal approximation of Poisson event variance.
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by research center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 93. HIV-1 Seroconversion Rates in Africa, mITT Population, Trial HPTN 083

Parameter	CAB (N=78)	TDF/FTC (N=74)	Result
Number of HIV-1 infected events	1	2	
PY of follow-up	93	97	
HIV-1 infection rate per 100 PY (95% CI)[1]	1.08 (0.03, 6.02)	2.07 (0.25, 7.48)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.63 (0.06, 6.50)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			27 (-550, 94)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] 95% CI was calculated using the normal approximation of Poisson event variance.
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by research center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CI, confidence interval; mITT, modified intention-to-treat, PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Subgroup Analyses by Ethnicity

There were two ethnicity groups in the trial, Hispanic or Latino and Not Hispanic or Latino. Results from both subgroups were similar to the overall mITT results.

Table 94. HIV-1 Seroconversion Rates in Hispanic or Latino, mITT Population, Trial HPTN 083

Parameter	CAB (N=1,041)	TDF/FTC (N=1,064)	Result
Number of HIV-1 infected events	6	14	
PY of follow-up	1,195	1,183	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.50 (0.18, 1.09)	1.18 (0.65, 1.99)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.45 (0.17, 1.15)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			55 (-15, 83)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] 95% CI was calculated using the normal approximation of Poisson event variance.
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by research center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 95. HIV-1 Seroconversion Rates in Not Hispanic or Latino, mITT Population, Trial HPTN 083

Parameter	CAB (N=1,239)	TDF/FTC (N=1,216)	Result
Number of HIV-1 infected events	7	25	
PY of follow-up	2,016	2,009	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.35 (0.14, 0.72)	1.24 (0.81, 1.84)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.28 (0.12, 0.65)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			72 (35, 88)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] 95% CI was calculated using the normal approximation of Poisson event variance.
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by research center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CI, confidence interval; mITT, modified intention-to-treat, PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

16.1.4. Additional Subgroup Analyses for Primary Efficacy Endpoint by Age and BMI at Baseline Using Updated mITT Population

Using the updated mITT population (two subjects were excluded from the original mITT and one of which was HIV-1 seroconversion), subgroup analyses by age, gender, race in United States, and region were conducted. Only results for age <30 years, MSM cohort, and region in Latin America subgroups were affected slightly. There results were used in the labeling.

Table 96. HIV-1 Seroconversion Rates by Subgroup, Updated mITT Population, Trial HPTN 083

	CAB				TDF/FTC				
Subgroup	Number of Subjects	Person-Years of Follow-Up	Number of HIV-1 Infected Events	HIV-1 Infection Rate /100 Person-Years (95% CI)[1]	Number of Subjects	Person-Years of Follow-Up	Number of HIV-1 Infected Events	HIV-1 Infection Rate /100 Person-Years (95% CI)[1]	Hazard Ratio (CAB vs. TDF/FTC) (95% CI)[2]
Age									
<30 years	1,568	2,110	10	0.47 (0.23, 0.87)	1,506	1,987	33	1.66 (1.14, 2.33)	0.29 (0.15, 0.59)
≥30 years	710	1,101	2	0.18 (0.02, 0.66)	775	1,206	6	0.50 (0.18, 1.08)	0.39 (0.08, 1.84)
Gender									
MSM	2,009	2,836	10	0.35 (0.17, 0.65)	1,976	2,803	32	1.14 (0.78, 1.61)	0.32 (0.16, 0.64)
TGW	266	371	2	0.54 (0.07, 1.95)	304	389	7	1.80 (0.72, 3.71)	0.34 (0.08, 1.56)
Race (in US)									
Black	412	691	4	0.58 (0.16, 1.48)	427	703	16	2.28 (1.30, 3.70)	0.26 (0.09, 0.76)
Non-Black	437	836	0	0.00 (0.00, 0.44)	421	801	4	0.50 (0.14, 1.28)	0.11 (0.00, 2.80)
Region									
US	849	1,528	4	0.26 (0.07, 0.67)	848	1,504	20	1.33 (0.81, 2.05)	0.21 (0.07, 0.60)
Latin America	976	1,020	5	0.49 (0.16, 1.14)	982	1,011	11	1.09 (0.54, 1.95)	0.47 (0.17, 1.35)
Asia	375	570	2	0.35 (0.04, 1.27)	377	581	6	1.03 (0.38, 2.25)	0.39 (0.08, 1.82)
Africa	78	93	1	1.08 (0.03, 6.02)	74	97	2	2.07 (0.25, 7.48)	0.63 (0.06, 6.50)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] 95% CI was calculated using the normal approximation of Poisson event variance.
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by research center.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat, MSM, cisgender men who have sex with men, TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; TGW, transgender women who have sex with men; US, United States

16.2. Additional Analyses for HPTN 084

16.2.1. Additional Analyses for Subject Disposition and Baseline Demographic and Clinical Characteristics

This section supplements the analyses and interpretation presented in Section 6.2.2.4.

The treatment status at the cutoff date using the ADSL dataset is listed below, which is slightly different from Table 3 in CSR which used the ADDS dataset. Approximately 94% of subjects in both arms had treatment ongoing. There were 52 subjects with category of "One or more reactive HIV test results or acute HIV infection suspected," 11 in CAB arm and 41 in TDF/FTC arm, which are the combination of the same category in completed due to seroconversion and discontinued from randomized treatment listed in Table 3 of the CSR. These are not the adjudicated primary endpoints.

Table 97. Patient Disposition of Treatment Status, Randomized Population, Trial HPTN 084

Randomized Treatment Status	CAB (N=1,614) n (%)	TDF/FTC (N=1,610) n (%)
Ongoing[1]	1,529 (94.7)	1,500 (93.2)
Discontinuation of treatment	85 (5.3)	110 (6.8)
Reasons of discontinuation		
Clinical AE (protocol mandated)	4	10
CMC recommendation based on a clinical event	3	1
CMC recommendation based on a laboratory value	3	1
Hepatitis B infection	1	1
Laboratory AE (protocol mandated)	14	18
Low oral adherence – Step 1	7	3
One or more reactive HIV-1 test results or acute HIV-1 infection suspected	11	41
Participant is currently using or planning to use PrEP or PEP (other than study product)	0	1
Participant refused long-acting contraception	10	10
Participant request – unwilling or unable to comply with required study procedures	19	6
Positive pregnancy test result	2	0
Other	11	18

Source: Statistical reviewer, ADSL and SAS software were used.
[1] Ongoing here includes treatment ongoing and maybe termination from study without discontinuation of treatment, which was listed in detail in Table 3 from ADDS.
Abbreviations: AE, adverse event; CAB, cabotegravir; CMC, clinical management committee; PEP, postexposure prophylaxis; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Participants status by Step is listed below. Approximately 94% of subjects in both arms entered the injection phase (Step 2) and about 2% of subjects in both arms entered Step 3 when the study was unblinded.

Table 98. Summary of Participants Status by Step, Randomized Population, TrialHPTN 084

Subject's Status by Step	CAB (N=1,614) n (%)	TDF/FTC (N=1,610) n (%)
Entered Step 1 (oral phase)	**1,614 (100)**	**1,610 (100)**
Still in Step 1 at cutoff date	48	52
Discontinued IP without termination of study during Step 1 (Entered annual follow-up during Step 1)	38	36
Terminated study during Step 1[1]	9	6
Completed Step 1 and entered Step 2	1,519 (94)	1,516 (94)
Entered Step 2 (injection phase)	**1,519 (94)**	**1,516 (94)**
Still in Step 2 at cutoff date	1,467	1,436
Discontinued IP without termination of study during Step 2 (entered Step 3 early)	39	37
Terminated study during Step 2[2]	13	43
Entered OLT Step 3	**39 (2)**	**36 (2)**
Still in OLT Step 3 at cutoff date	25	25
Completed OLT Step 3 (who have been followed for 48 weeks)	8	9
Terminated study during OLT Step 3	6	2

Source: Statistical reviewer, ADDS and SAS software were used.
[1] Terminated study during Step 1 includes completed Step 1 due to seroconversion during Step 1, terminated study during Step 1 either discontinued IP or w/o an IP discontinuation.
[2] Terminated study during Step 2 includes completed Step 2 due to seroconversion during Step 1, terminated study during Step 2 either discontinued IP or w/o an IP discontinuation.
Abbreviations: CAB, cabotegravir; IP, investigational product; OLT, open-label TDF/FTC; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 99 lists some additional baseline demographic and clinical characteristics.

Table 99. Some Additional Baseline Demographic and Clinical Characteristics, mITT Population, Trial HPTN 084

Characteristics	CAB	TDF/FTC	Total
mITT population			
n	1,614	1,610	3,224
Weight (kg) at baseline			
Mean (SD)	68.5 (16.4)	67.7 (15.8)	68.1 (16.1)
Median (Q1, Q3)	66 (56, 78)	65 (56, 77)	65 (56, 78)
(Min, Max)	(39, 148)	(35, 128)	(35, 148)
Height (CM) at baseline			
Mean (SD)	159.4 (6.6)	159.1 (6.4)	159.2 (6.5)
Median (Q1, Q3)	159 (155, 164)	159 (155, 163)	159 (155, 164)
(Min, Max)	(114, 188)	(131, 187)	(114, 188)
BMI at baseline			
Mean (SD)	26.97 (6.20)	26.75 (5.95)	26.86 (6.08)
Median (Q1, Q3)	25.70 (22.3, 30.9)	25.60 (22.2, 30.1)	25.65 (22.2, 30.5)
(Min, Max)	(16.4, 54.3)	(15.0, 51.3)	(15.0, 54.3)
Marriage status			
Have primary or main partner, not living together	869 (53.8%)	860 (53.4%)	1,729 (53.6%)
Living with primary or main partner	106 (6.6%)	118 (7.3%)	224 (6.9%)
Married/Civil/Legal partnership	169 (10.5%)	174 (10.8%)	343 (10.6%)
Single/Divorced/Widowed	465 (28.8%)	454 (28.2%)	919 (28.5%)
Other	5 (0.3%)	4 (0.2%)	9 (0.3%)

Characteristics	CAB	TDF/FTC	Total
Education level			
No schooling	20 (1.2%)	12 (0.7%)	32 (1.0%)
Primary school, complete	96 (5.9%)	92 (5.7%)	188 (5.8%)
Primary school, not complete	155 (9.6%)	163 (10.1%)	318 (9.9%)
Secondary school, complete	578 (35.8%)	600 (37.3%)	1,178 (36.5%)
Secondary school, not complete	576 (35.7%)	582 (36.1%)	1,158 (35.9%)
Technical training, complete	24(1.5%)	17 (1.1%)	41 (1.3%)
Technical training, not complete	24 (1.5%)	24 (1.5%)	48 (1.5%)
College/University or higher, complete	41 (2.5%)	31 (1.9%)	72 (2.2%)
College/University or higher, not complete	100 (6.2%)	89 (5.5%)	189 (5.9%)
Job status			
Full-time employment	236 (14.6%)	220 (13.7%)	456 (14.1%)
Not employed	1,163 (72.1%)	1,183 (73.5%)	2,346 (72.8%)
Part-time employment	215 (13.3%)	207 (12.9%)	422 (13.1%)
Site			
548	76 (4.7%)	75 (4.7%)	151 (4.7%)
720	56 (3.5%)	55 (3.4%)	111 (3.4%)
723	46 (2.9%)	45 (2.8%)	91 (2.8%)
753	102 (6.3%)	102 (6.3%)	204 (6.3%)
754	80 (5.0%)	80 (5.0%)	160 (5.0%)
760	57 (3.5%)	56 (3.5%)	113 (3.5%)
762	84 (5.2%)	82 (5.1%)	166 (5.1%)
770	76 (4.7%)	77 (4.8%)	153 (4.7%)
771	69 (4.3%)	69 (4.3%)	138 (4.3%)
774	82 (5.1%)	80 (5.0%)	162 (5.0%)
779	112 (6.9%)	111 (6.9%)	223 (6.9%)
789	110 (6.8%)	113 (7.0%)	223 (6.9%)
792	31 (1.9%)	35 (2.2%)	66 (2.0%)
802	89 (5.5%)	87 (5.4%)	176 (5.5%)
803	85 (5.3%)	85 (5.3%)	170 (5.3%)
818	78 (4.8%)	81 (5.0%)	159 (4.9%)
837	103 (6.4%)	103 (6.4%)	206 (6.4%)
871	80 (5.0%)	80 (5.0%)	160 (5.0%)
872	105 (6.5%)	105 (6.5%)	210 (6.5%)
873	93 (5.8%)	89 (5.5%)	182 (5.6%)

Source: Statistical reviewer, ADSL and SAS software were used.
Abbreviations: CAB, cabotegravir; mITT, modified intention-to-treat; N, number of participants in treatment group; n, number of participants with given characteristic; SD, standard deviation; SE, standard error; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

16.2.2. Sensitivity Analyses of the Primary Efficacy Endpoint

The primary efficacy endpoint results were consistent across sensitivity analyses presented below.

The first sensitivity analysis used the injection Step 2 efficacy population for the primary endpoint analysis, which includes mITT population subjects who received at least one injection, were not infected at the time of the first injection (Step 1 infections were excluded) and had at least one follow-up visit with nonmissing HIV-1 test results after the first injection. The follow-up time started from beginning of injection. As a result, the number of subjects, number of infections, and PY of follow-up in both arms decreased (see Table 100).

The HR estimate was 0.06 with 95% CI (0.01, 0.24), and the seroconversion rate reduction estimate was 94% with 95% CI (76%, 99%), which confirmed Table 18 in the CSR.

Table 100. HIV-1 Seroconversion Rates and Hazard Ratio, Step 1 and 2, Injection Step 2 Efficacy Population, Trial HPTN 084

Parameter	CAB (N=1,495)	TDF/FTC (N=1,494)	Results
Number of HIV-1 infected events	2	34	
PY of follow-up	1,766	1,750	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.11 (0.01, 0.41)	1.94 (1.35, 2.72)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.06 (0.01, 0.24)
Superiority test p-value			<0.0001
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			94 (76, 99)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

The second sensitivity analysis used the OBSP population for the primary endpoint analysis, which includes injection Step 2 efficacy population subjects. The follow-up time was counted while subjects were compliant to the injection schedule and was censored at the first time of a delayed/missed injection. As a result, the number of infections, and PY of follow-up in both arms decreased compared to the primary efficacy analysis results (see Table 101).

The HR estimate was 0.05 with 95% CI (0.01, 0.37), and the seroconversion rate reduction estimate was 95% with 95% CI (63%, 99%), which confirmed Table 17 in the CSR.

Table 101. HIV-1 Seroconversion Rates and Hazard Ratio, Step 1 and 2, On Blinded Study Product (OBSP) Population, Trial HPTN 084

Parameter	CAB (N=1,495)	TDF/FTC (N=1,494)	Results
Number of HIV-1 infected events	1	20	
PY of follow-up	1,413	1,431	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.07 (0.00, 0.39)	1.40 (0.85, 2.16)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.05 (0.01, 0.37)
Superiority test p-value			0.0034
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			95 (63, 99)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

In the third sensitivity analysis, the follow-up times for infected subjects were calculated as the number of days between enrollment and the first positive HIV-1 test results as determined by the EAC, instead of the number of days between enrollment and the midpoint between the last HIV-1 negative visit and first HIV-1 positive visit, as determined by the EAC. As a result, the number of PY of follow-up in TDF/FTC arm increased by approximately 2 years (see Table 102).

The HR estimate was 0.11 with 95% CI (0.04, 0.31), and the seroconversion rate reduction estimate was 89% with 95% CI (69%, 96%), which are almost identical to the primary efficacy analysis results.

Table 102. HIV-1 Seroconversion Rates and Hazard Ratio, Step 1 and 2 Using the First Positive HIV-1 Test Date as the End of Follow-Up Time, mITT Population, Trial HPTN 084

Parameter	CAB (N=1,614)	TDF/FTC (N=1,610)	Results
Number of HIV-1 infected events	4	36	
PY of follow-up	1,961	1,948	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.20 (0.06, 0.52)	1.85 (1.29, 2.56)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.109 (0.04, 0.31)
Superiority test p-value			<0.0001
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			89 (69, 96)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

An Additional Baseline Infection Identified After the Primary Efficacy Analysis

In the SN0019 submission under this NDA submission, the Applicant submitted supplemental virology report for HPTN 084. Retrospective extended virologic testing performed for HPTN 084 seroconverters by the HPTN Laboratory Center revealed that one of the four cases originally identified on the CAB arm as an incident HIV-1 infection (defined as acquisition of HIV-1 infection after enrollment) based on site-level testing was readjudicated as a prevalent infection based on retrospective laboratory center testing.

- Subject 300084-(b) (6), who was in original mITT population as a seroconverter infected in Step 2 with 0.55 years of follow-up, was identified retrospectively as baseline infections. The updated mITT population includes all subjects from original mITT except Subject 300084-(b) (6).

Using the updated mITT population, the updated primary endpoint analysis results are listed below. The results were similar to the primary efficacy results with a slightly lower seroconversion rate in the CAB arm and a slightly lower HR. The bias-adjusted HR was 0.10 with 95% CI (0.04, 0.27) and the seroconversion rate reduction estimate was 90% with 95% CI (73%, 96%).

Table 103. HIV-1 Seroconversion Rates and Hazard Ratio, Step 1 and 2, Updated mITT Population, Trial HPTN 084

Parameter	CAB (N=1,613)	TDF/FTC (N=1,610)	Results
Number of HIV-1 infected events	3	36	
PY of follow-up	1,960	1,946	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.15 (0.03, 0.45)	1.85 (1.30, 2.56)	
Cox regression results			
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.08 (0.03, 0.27)
Superiority test p-value			<0.0001
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			92 (73, 97)
Bias-adjusted, corrected for early stopping[4]			
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.10 (0.04, 0.27)

Parameter	CAB (N=1,613)	TDF/FTC (N=1,610)	Results
Superiority test p-value			<0.0001
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			90 (73, 96)

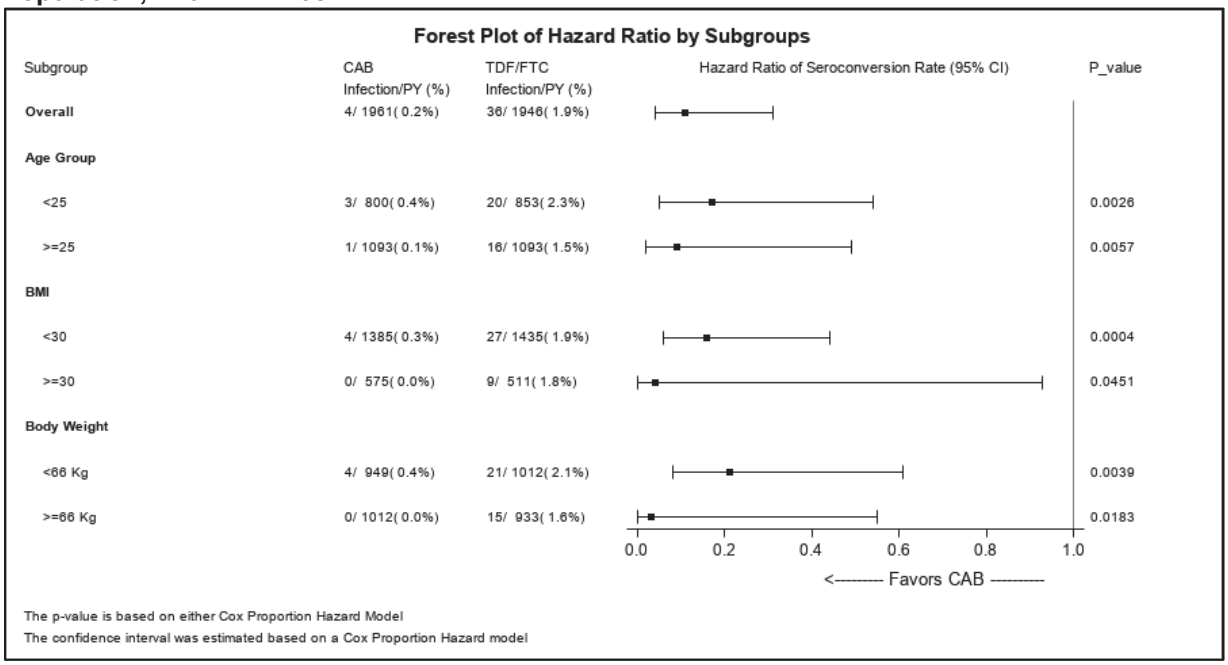
Source: Statistical reviewer, ADSL, ADTTE, the clinical-info-amend-084-virol.pdf in SN0019, and SAS software were used.
[1] Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
[4] The bias-adjusted hazard ratio, CI and p-value account for the group-sequential trial design and the early stopping time with updated information fraction.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

16.2.3. Additional Subgroup Analyses for Primary Efficacy Endpoint

This section supplements the analyses and interpretation presented in Section 6.2.2.4. Of note, the sample sizes for many subgroups were small, which limits the ability to detect trends with certainty. Numerous subgroup analyses were conducted without any adjustment for the multiple analyses, which could result in spurious findings due to chance.

The subgroups analyzed were age groups, BMI index, and baseline body weight. The results of subgroups analyzed were similar to overall results (Figure 16).

Figure 16. Forest Plot of Subgroup Analyses Results of Primary Efficacy Endpoint, mITT Population, Trial HPTN 084



Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
Abbreviations: CAB, cabotegravir; CI, confidence interval; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Subgroup Analyses by Age

The age subgroup was categorized as age <25 years and ≥25 years. The results from both age groups were very similar to the overall mITT results with a HR of 0.17, 95% CI (0.05, 0.54) and

a risk reduction of 83% for <25 age group, and a HR of 0.09, 95% CI (0.02, 0.49) and a risk reduction of 91% for ≥25 age group.

Table 104. HIV-1 Seroconversion Rates in Age <25 Years, mITT Population, Trial HPTN 084

Parameter	CAB (N=800)	TDF/FTC (N=794)	Result
Number of HIV-1 infected events	3	20	
PY of follow-up	868	853	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.35 (0.07, 1.01)	2.34 (1.43, 3.62)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.17 (0.05, 0.54)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			83 (46, 95)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 105. HIV-1 Seroconversion Rates in Age ≥25 Years, mITT Population, Trial HPTN 084

Parameter	CAB (N=814)	TDF/FTC (N=816)	Result
Number of HIV-1 infected events	1	16	
PY of follow-up	1,093	1,093	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.09 (0.00, 0.51)	1.46 (0.84, 2.38)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.09 (0.02, 0.49)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			91 (51, 98)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Subgroup Analyses by BMI Index at Baseline

The BMI subgroup was categorized as baseline BMI <30 and ≥30. Results from both subgroups were very similar to the overall mITT results. The 95% CI of the HR in the BMI ≥30 subgroup was much wider than that in the overall mITT population and in the BMI <30 subgroup due to the smaller sample sizes.

Table 106. HIV-1 Seroconversion Rates in Baseline BMI <30, mITT Population, Trial HPTN 084

Parameter	CAB (N=1,149)	TDF/FTC (N=1,180)	Result
Number of HIV-1 infected events	4	27	
PY of follow-up	1,385	1,435	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.29 (0.08, 0.74)	1.88 (1.24, 2.74)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.16 (0.06, 0.44)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			84 (56, 94)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] 95% CI was calculated using the normal approximation of Poisson event variance.
[2] Hazard ratio and 95% CI were estimated based on a Cox proportional hazard model stratified by research center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; MSM, men having sex with men; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; TGW, transgender women

Table 107. HIV-1 Seroconversion Rates in Baseline BMI ≥30, mITT Population, Trial HPTN 084

Parameter	CAB (N=465)	TDF/FTC (N=430)	Result
Number of HIV-1 infected events	0	9	
PY of follow-up	575	511	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.00 (0.00, 0.64)	1.76 (0.81, 3.35)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.04 (0.00, 0.93)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			96 (7, 100)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] 95% CI was calculated using the normal approximation of Poisson event variance.
[2] Hazard ratio and 95% CI were estimated based on a Cox proportional hazard model stratified by research center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: BMI, body mass index; CI, confidence interval; mITT, modified intention-to-treat; MSM, men having sex with men; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Subgroup Analyses by Baseline Body Weight

The body weight subgroup was categorized as baseline body weight <66 kg and ≥66 kg. Results from both subgroups were very similar to the overall mITT results.

Table 108. HIV-1 Seroconversion Rates in Baseline Body Weight <66 kg, mITT Population, Trial HPTN 084

Parameter	CAB (N=801)	TDF/FTC (N=840)	Result
Number of HIV-1 infected events	4	21	
PY of follow-up	949	1,012	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.42 (0.11, 1.08)	2.07 (1.28, 3.17)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.21 (0.08, 0.61)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			79 (39, 92)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] 95% CI was calculated using the normal approximation of Poisson event variance.
[2] Hazard ratio and 95% CI were estimated based on a Cox proportional hazard model stratified by research center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 109. HIV-1 Seroconversion Rates in Baseline Body Weight ≥66 kg, mITT Population, Trial HPTN 084

Parameter	CAB (N=813)	TDF/FTC (N=770)	Result
Number of HIV-1 infected events	0	15	
PY of follow-up	1,012	933	
HIV-1 infection rate per 100 PY (95% CI)[1]	0.00 (0.00, 0.36)	1.61 (0.90, 2.65)	
Hazard ratio (CAB vs. TDF/FTC) (95% CI)[2]			0.03 (0.00, 0.55)
Percentage reduction in HIV-1 seroconversion rate (95% CI)[3]			97 (45, 100)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] 95% CI was calculated using the normal approximation of Poisson event variance.
[2] Hazard ratio and 95% CI were estimated based on a Cox proportional hazard model stratified by research center.
[3] Percentage of reduction = (1 – Hazard ratio)*100.
Abbreviations: CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; PY, person-year(s); TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

16.2.4. Subgroup Analyses for Primary Efficacy Endpoint by Age and BMI at Baseline Using Updated mITT population

Using the updated mITT population (one subject who was HIV-1 seroconverted and was excluded from the original mITT), subgroup analyses by age and BMI index at baseline were conducted. Only results for age <25 years and BMI <30 subgroups were affected slightly. There results were used in the labeling.

Table 110. HIV-1 Seroconversion Rates by Subgroup, Updated mITT Population, Trial HPTN 084

	CAB				TDF/FTC				
Subgroup	Number of Subjects	Person-Years of Follow-Up	Number of HIV-1 Infected Events	HIV-1 Infection Rate /100 Person-Years (95% CI)[1]	Number of Subjects	Person-Years of Follow-Up	Number of HIV-1 Infected Events	HIV-1 Infection Rate /100 Person-Years (95% CI)[1]	Hazard Ratio (CAB vs. TDF/FTC) (95% CI)[2]
Age									
<25 years	799	868	2	0.23 (0.03, 0.83)	794	853	20	2.34 (1.43, 3.62)	0.12 (0.03, 0.46)
≥25 years	814	1,093	1	0.09 (0.00, 0.51)	816	1,093	16	1.46 (0.84, 2.38)	0.09 (0.02, 0.49)
BMI									
<30	1,148	1,385	3	0.22 (0.08, 0.74)	1,180	1,435	27	1.88 (1.24, 2.74)	0.12 (0.04, 0.38)
≥30	465	575	0	0.00 (0.00, 0.64)	430	511	9	1.76 (0.81, 3.35)	0.04 (0.00, 0.93)

Source: Statistical reviewer, ADSL, ADTTE and SAS software were used.
[1] Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
[2] Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazard model stratified by center.
Abbreviations: BMI, body mass index; CAB, cabotegravir; CI, confidence interval; mITT, modified intention-to-treat; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

16.3. Patient-Reported Outcomes

In both HPTN 083 and HPTN 084 the acceptability and preferences for CAB LA versus oral TDF/FTC were compared as a secondary endpoint. As described in Section 4, participants in HPTN 083 completed a SMSQ at various time points throughout the trial. As shown in Table 111, satisfaction scores were similar among CAB and TDF/FTC participants; however, the mean satisfaction score was slightly higher among TDF/FTC participants at all time points .

Regarding preference, at Week 41 the majority of participants (66% of participants in both arms) reported no preference in terms of convenience. Regarding preference in terms of pain or discomfort experienced with study medication, most participants reported “no preference” (CAB: 483/1,589 [30%] participants; TDF/FTC: 726/1,591[46%] participants) or “prefers oral” (CAB: 1,047/1,589 [66%] participants; TDF/FTC: 766/1,591 [48%] participants). A very small minority of patients preferred injection.

In HPTN 084, the SMSQ was not used. Instead, overall treatment satisfaction was assessed by asking participants about inconvenience and pain or discomfort experienced with receiving the oral and injectable study medication. The majority (68%) of participants in both arms reported that there was no inconvenience or difficulty for the injectable study product. However, pain was more commonly reported with the injections among CAB participants than among TDF/FTC participants.

These findings suggest that the local injection site pain/discomfort associated with CAB LA may be a deterrent for some patients but not others, highlighting the need for options for different routes of PrEP administration.

Table 111. Summary of SMSQ Score by Visit, Injection Safety Population, Trial HPTN 083

	CAB (N=2281)	TDF/FTC (N=2285)
SMSQs Overall Score		
Week 6		
n	1830	1791
Mean (SD)	56.4 (11.13)	60.8 (6.79)
Median	60.0	64.0
Minimum, Maximum	0, 66	6, 66
Week 10		
n	1752	1727
Mean (SD)	57.0 (10.99)	61.0 (7.26)
Median	61.0	64.0
Minimum, Maximum	0, 66	0, 66
Week 51		
n	1193	1194
Mean (SD)	59.8 (8.59)	62.0 (6.43)
Median	63.0	65.0
Minimum, Maximum	0, 66	11, 66
Week 59		
n	1094	1083
Mean (SD)	60.0 (8.54)	62.3 (5.70)
Median	63.0	66.0
Minimum, Maximum	0, 66	26, 66
Step 3 – Day 0		
n	14	5
Mean (SD)	34.8 (22.77)	58.2 (8.47)
Median	33.0	63.0
Minimum, Maximum	0, 66	49, 66

	CAB (N=2281)	TDF/FTC (N=2285)
SMSQc Overall Score		
Week 19		
n	1657	1652
Mean (SD)	21.6 (12.83)	23.5 (11.73)
Median	27.0	29.0
Minimum, Maximum	-33, 33	-33, 33

Source: Table 71 is the HPTN 083 CSR
Abbreviations: CAB, cabotegravir; SD, standard deviation; SMSQ, Study Medication Satisfaction Questionnaire; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

17. Clinical Safety: Additional Information and Assessment

This review section contains supplemental safety analyses not included in the integrated review Section 7.6, and additional analyses supporting the safety conclusions included in Section II.

17.1. Deaths, HPTN 083 and HPTN 084

The following table provides additional details regarding the deaths in CAB participants in HPTN 083.

Table 112. Summary of Narratives for Participants With a Fatal Adverse Event in the Cabotegravir (CAB) Arm, Safety Population, Trial HPTN 083

Subject ID	Assessment of Causality		
Age/Sex	Investigator	Reviewer	Summary of Event
(b) (6) 18/M	Not related	Not related	Gunshot wound Approximately 1 year after starting CAB, this 19-year-old was found dead in the street. Autopsy was performed and internal bleeding due to gunshot wound was the established cause of death.
(b) (6) 30/M	Not related	Not related	Traumatic hemorrhage A 31-year-old man with a history of depression and alcohol, illicit drug, and tobacco use was found dead in his home 174 days after starting CAB. The cause of death on the death certificate was listed as “firing of another firearm and unspecified firearm.” The verbatim term was updated to “homicide.”
(b) (6) 32/M	Not related	Not related	Asphyxia Approximately 14 months after starting CAB, a 34-year-old male developed fatal mechanical asphyxia due to respiratory tract obstruction. At his most recent study visit, approximately 2 weeks earlier, the participant was asymptomatic and in good general health. No concomitant medications were reported at that visit.
(b) (6) 22/M	Not related	Not related	Cardiopulmonary failure A 23-year-old male with a history of appendectomy, rhinoplasty, and tonsillectomy was found dead in his apartment by a police officer. He had no reported history of alcohol use or illicit drug use and no known family history. A partial autopsy was performed, and the cause of death was reported as cardiorespiratory failure with no apparent cause of death in a decomposed body. No toxicology report was available. However, a friend later reported that a syringe of methamphetamine was found next to the participant when he was found dead.

Source: Case narratives in Applicant’s CSR.

17.2. Serious Adverse Events, HPTN 083 and HPTN 084

Sections 7.6.1.3 and 7.6.2.3 present drug-related SAEs. Below is a complete tabulation of SAEs, regardless of causality, for each trial.

Table 113 Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial HPTN 083

System Organ Class Preferred Term	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Blood and lymphatic system disorders (SOC)	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Immune thrombocytopenia	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Cardiac disorders (SOC)	0	4 (0.2)	0	6 (0.3)	-0.1 (-0.4, 0.2)
Acute myocardial infarction	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Arrhythmia	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Atrial fibrillation	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Atrial flutter	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Cardiac disorder	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Cardiopulmonary failure	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Myocardial infarction	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Myocardial ischemia	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Congenital, familial and genetic disorders (SOC)	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Thyroglossal cyst	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Ear and labyrinth disorders (SOC)	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Vertigo	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Eye disorders (SOC)	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Ulcerative keratitis	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Gastrointestinal disorders (SOC)	0	4 (0.2)	0	6 (0.3)	-0.1 (-0.4, 0.2)
Alcoholic pancreatitis	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Anal fissure	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Anal fistula	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Cannabinoid hyperemesis syndrome	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Enteritis	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Food poisoning	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Gastritis	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Hemorrhoids	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Hemorrhoids thrombosed	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Intussusception	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Pancreatitis	0	0	0	2 (0.1)	-0.1 (-0.2, 0.0)
General disorders and administration site conditions (SOC)	0	2 (0.09)	0	1 (0.05)	0.0 (-0.1, 0.2)
Pyrexia	0	2 (0.09)	0	1 (0.05)	0.0 (-0.1, 0.2)
Hepatobiliary disorders (SOC)	0	0	1 (0.04)	1 (0.05)	-0.0 (-0.1, 0.0)
Cholecystitis	0	0	1 (0.04)	0	0 (0, 0)
Cholecystitis acute	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)

System Organ Class Preferred Term	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Infections and infestations (SOC)	3 (0.1)	42 (2.0)	2 (0.09)	35 (1.7)	0.3 (-0.5, 1.1)
Abscess limb	0	2 (0.09)	0	0	0.1 (-0.0, 0.2)
Acute hepatitis B	0	2 (0.09)	0	0	0.1 (-0.0, 0.2)
Cellulitis	0	3 (0.1)	0	1 (0.05)	0.1 (-0.1, 0.3)
Influenza	0	4 (0.2)	0	2 (0.1)	0.1 (-0.1, 0.3)
Pharyngitis	0	2 (0.09)	0	0	0.1 (-0.0, 0.2)
Abdominal abscess	0	0	1 (0.04)	0	0 (0, 0)
Acute hepatitis C	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Anal abscess	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Arthritis gonococcal	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Bronchitis	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Dengue fever	1 (0.04)	4 (0.2)	0	3 (0.1)	0.0 (-0.2, 0.3)
Dengue hemorrhagic fever	0	2 (0.09)	0	1 (0.05)	0.0 (-0.1, 0.2)
Febrile infection	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Hepatitis A	0	2 (0.09)	1 (0.04)	1 (0.05)	0.0 (-0.1, 0.2)
Kidney infection	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Lymphogranuloma venereum	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Nasopharyngitis	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Osteomyelitis	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Parotitis	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Pharyngotonsillitis	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Pneumonia	0	3 (0.1)	0	3 (0.1)	-0.0 (-0.2, 0.2)
Pneumonia bacterial	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Pulmonary tuberculosis	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Pyelonephritis acute	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Respiratory tract infection viral	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Secondary syphilis	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Shigella infection	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Sinusitis	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Tonsillitis	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Tonsillitis bacterial	1 (0.04)	0	0	0	0 (0, 0)
Tooth abscess	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Upper respiratory tract infection	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Viral pericarditis	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Gastroenteritis	0	2 (0.09)	0	5 (0.2)	-0.1 (-0.4, 0.1)
Appendicitis	1 (0.04)	2 (0.09)	1 (0.04)	7 (0.3)	-0.2 (-0.5, 0.0)
Injury, poisoning and procedural complications (SOC)	1 (0.04)	12 (0.6)	2 (0.09)	21 (1.0)	-0.4 (-1.0, 0.1)
Ankle fracture	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Burns second degree	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Comminuted fracture	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Concussion	0	3 (0.1)	0	2 (0.1)	0.0 (-0.2, 0.3)
Craniocerebral injury	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Extradural hematoma	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Foreign body in gastrointestinal tract	0	1 (0.05)	1 (0.04)	0	0.0 (-0.0, 0.1)
Gunshot wound	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)

System Organ Class Preferred Term	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Head injury	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Hip fracture	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Injury	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Intentional overdose	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Jaw fracture	1 (0.04)	0	0	0	0 (0, 0)
Lower limb fracture	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Multiple fractures	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Multiple injuries	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Muscle strain	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Post-concussion syndrome	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Post procedural complication	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Skin abrasion	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Soft tissue injury	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Stab wound	0	0	1 (0.04)	1 (0.05)	-0.0 (-0.1, 0.0)
Tendon injury	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Tendon rupture	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Tibia fracture	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Traumatic hemorrhage	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Meniscus injury	0	0	0	2 (0.1)	-0.1 (-0.2, 0.0)
Investigations (SOC)	0	0	0	3 (0.1)	-0.1 (-0.3, 0.0)
Alanine aminotransferase increased	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Blood creatine phosphokinase increased	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Lipase increased	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Metabolism and nutrition disorders (SOC)	0	2 (0.09)	0	0	0.1 (-0.0, 0.2)
Hyperglycemia	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Hypokalemia	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Musculoskeletal and connective tissue disorders (SOC)	1 (0.04)	2 (0.09)	0	2 (0.1)	-0.0 (-0.2, 0.2)
Arthralgia	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Intervertebral disc protrusion	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Rhabdomyolysis	1 (0.04)	0	0	0	0 (0, 0)
Spinal osteoarthritis	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Systemic lupus erythematosus	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	3 (0.1)	0	0	0.1 (-0.0, 0.3)
Extranodal marginal zone B-cell lymphoma (MALT type)	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Metastatic carcinoma of the bladder	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Renal cell carcinoma	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)

System Organ Class Preferred Term	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Nervous system disorders (SOC)	0	5 (0.2)	1 (0.04)	3 (0.1)	0.1 (-0.2, 0.4)
Seizure	0	2 (0.09)	1 (0.04)	0	0.1 (-0.0, 0.2)
Brain stem infarction	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Cerebral hemorrhage	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Dizziness	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Lumbar radiculopathy	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Sciatica	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Status epilepticus	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Psychiatric disorders (SOC)	4 (0.2)	17 (0.8)	7 (0.3)	19 (0.9)	-0.1 (-0.7, 0.4)
Acute stress disorder	0	0	1 (0.04)	0	0 (0, 0)
Adjustment disorder	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Affective disorder	1 (0.04)	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Aggression	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Alcoholism	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Bipolar disorder	0	0	1 (0.04)	0	0 (0, 0)
Borderline personality disorder	0	0	1 (0.04)	0	0 (0, 0)
Depression suicidal	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Impulse-control disorder	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Major depression	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Post-traumatic stress disorder	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Psychotic disorder	0	0	1 (0.04)	0	0 (0, 0)
Substance-induced psychotic disorder	1 (0.04)	0	0	0	0 (0, 0)
Substance abuse	1 (0.04)	0	0	0	0 (0, 0)
Suicidal ideation	0	6 (0.3)	0	6 (0.3)	-0.0 (-0.3, 0.3)
Depression	0	2 (0.09)	2 (0.09)	4 (0.2)	-0.1 (-0.3, 0.1)
Suicide attempt	2 (0.09)	5 (0.2)	1 (0.04)	9 (0.4)	-0.2 (-0.5, 0.2)
Renal and urinary disorders (SOC)	0	1 (0.05)	0	2 (0.1)	-0.0 (-0.2, 0.1)
Nephrolithiasis	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Renal colic	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Ureterolithiasis	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.04)	3 (0.1)	0	0	0.1 (-0.0, 0.3)
Apnea	1 (0.04)	0	0	0	0 (0, 0)
Asphyxia	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Pneumonia aspiration	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Respiratory distress	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Skin and subcutaneous tissue disorders (SOC)	0	2 (0.09)	0	0	0.1 (-0.0, 0.2)
Stevens-Johnson syndrome	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Urticaria	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)

System Organ Class Preferred Term	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Vascular disorders (SOC)	0	0	0	3 (0.1)	-0.1 (-0.3, 0.0)
Vascular occlusion	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Deep vein thrombosis	0	0	0	2 (0.1)	-0.1 (-0.2, 0.0)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE after the first dose of study drug and until 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively). For those with no injections, events after the first of 1 day after the date of discontinuation or 120 days after randomization were considered not treatment-emergent.
Duration is median 29 days for Step 1 groups and median 457 days for Step 2 groups.
Risk difference column shows difference (with 95% confidence interval) between step 2 groups.
Abbreviations: CAB, cabotegravir; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 114. Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial HPTN 084

System Organ Class Preferred Term	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Blood and lymphatic system disorders (SOC)	0	0	1 (0.06)	0	0 (0, 0)
Hypersplenism	0	0	1 (0.06)	0	0 (0, 0)
Gastrointestinal disorders (SOC)	0	0	1 (0.06)	1 (0.07)	-0.1 (-0.2, 0.1)
Peptic ulcer	0	0	1 (0.06)	1 (0.07)	-0.1 (-0.2, 0.1)
Hepatobiliary disorders (SOC)	0	1 (0.07)	1 (0.06)	1 (0.07)	-0.0 (-0.2, 0.2)
Hepatitis acute	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Hepatotoxicity	0	0	1 (0.06)	0	0 (0, 0)
Hepatitis alcoholic	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Infections and infestations (SOC)	1 (0.06)	11 (0.7)	2 (0.1)	9 (0.6)	0.1 (-0.4, 0.7)
Malaria	0	5 (0.3)	2 (0.1)	1 (0.07)	0.3 (-0.1, 0.6)
COVID-19	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Endometritis	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Gastritis bacterial	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Hepatitis A	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Peritonsillar abscess	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Respiratory tract infection	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Bartholin's abscess	1 (0.06)	0	0	0	0 (0, 0)
Urinary tract infection	0	0	1 (0.06)	0	0 (0, 0)
Appendiceal abscess	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Escherichia pyelonephritis	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Pelvic inflammatory disease	0	1 (0.07)	0	2 (0.1)	-0.1 (-0.3, 0.2)
Pneumonia bacterial	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Pulmonary tuberculosis	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Tonsillitis bacterial	0	0	0	2 (0.1)	-0.1 (-0.3, 0.1)

System Organ Class Preferred Term	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Injury, poisoning and procedural complications (SOC)	0	3 (0.2)	0	5 (0.3)	-0.1 (-0.5, 0.2)
Arthropod sting	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Post-concussion syndrome	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Soft tissue injury	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Head injury	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Humerus fracture	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Intentional overdose	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Skin laceration	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Stab wound	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Investigations (SOC)	0	1 (0.07)	0	3 (0.2)	-0.1 (-0.4, 0.1)
Alanine aminotransferase increased	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Aspartate aminotransferase increased	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Blood creatine phosphokinase increased	0	1 (0.07)	0	2 (0.1)	-0.1 (-0.3, 0.2)
Metabolism and nutrition disorders (SOC)	0	1 (0.07)	1 (0.06)	1 (0.07)	-0.0 (-0.2, 0.2)
Diabetic ketoacidosis	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Hypoglycemia	0	0	1 (0.06)	0	0 (0, 0)
Diabetes mellitus	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Musculoskeletal and connective tissue disorders (SOC)	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Lumbar spinal stenosis	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Uterine leiomyoma	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Nervous system disorders (SOC)	0	2 (0.1)	1 (0.06)	0	0.1 (-0.1, 0.3)
Cerebrovascular accident	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Headache	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Seizure	0	0	1 (0.06)	0	0 (0, 0)
Pregnancy, puerperium and perinatal conditions (SOC)	0	1 (0.07)	0	1 (0.07)	-0.0 (-0.2, 0.2)
Ectopic pregnancy	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Ruptured ectopic pregnancy	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Psychiatric disorders (SOC)	0	3 (0.2)	1 (0.06)	4 (0.3)	-0.1 (-0.4, 0.3)
Anxiety	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Panic disorder	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Depression	0	1 (0.07)	0	1 (0.07)	-0.0 (-0.2, 0.2)
Intentional self-injury	0	1 (0.07)	0	1 (0.07)	-0.0 (-0.2, 0.2)
Major depression	0	0	1 (0.06)	0	0 (0, 0)
Psychotic disorder	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Suicide attempt	0	0	0	2 (0.1)	-0.1 (-0.3, 0.1)

System Organ Class Preferred Term	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Reproductive system and breast disorders (SOC)	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Dysfunctional uterine bleeding	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE with an onset date on or after the start of treatment and before 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively).
Duration is median 29 days for Step 1 groups and median 452 days for Step 2 groups.
Risk difference column shows difference (with 95% confidence interval) between step 2 groups.
Abbreviations: CAB, cabotegravir; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

17.3. Treatment-Emergent Adverse Events, HPTN 083 and HPTN 084

Sections 7.6.1.5 and 7.6.2.5 present drug-related treatment-emergent AEs (TEAEs). Below is a tabulation of TEAEs occurring in at least 1% of participants, regardless of causality, for each trial.

Table 115. Common Adverse Events Occurring at ≥1% Frequency, Safety Population, Trial HPTN 083

Preferred Term	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Any AE	1,508 (66.1)	2,072 (97.9)	1,564 (68.4)	2,009 (96.5)	1.3 (0.3, 2.3)
Injection site pain	1 (0.04)	1,713 (80.9)	7 (0.3)	686 (33.0)	48.0 (45.3, 50.6)
Injection site nodule	0	263 (12.4)	0	13 (0.6)	11.8 (10.4, 13.2)
Injection site induration	0	255 (12.0)	1 (0.04)	7 (0.3)	11.7 (10.3, 13.1)
Injection site swelling	0	206 (9.7)	0	9 (0.4)	9.3 (8.0, 10.6)
Pyrexia	20 (0.9)	221 (10.4)	17 (0.7)	100 (4.8)	5.6 (4.0, 7.2)
Blood glucose increased	44 (1.9)	226 (10.7)	27 (1.2)	149 (7.2)	3.5 (1.8, 5.2)
Injection site erythema	0	63 (3.0)	0	11 (0.5)	2.4 (1.7, 3.2)
Injection site warmth	0	60 (2.8)	0	9 (0.4)	2.4 (1.6, 3.2)
Injection site bruising	0	63 (3.0)	0	26 (1.2)	1.7 (0.9, 2.6)
Low density lipoprotein increased	2 (0.09)	66 (3.1)	0	30 (1.4)	1.7 (0.8, 2.6)
Malaise	4 (0.2)	54 (2.6)	6 (0.3)	17 (0.8)	1.7 (1.0, 2.5)
Hypertension	17 (0.7)	100 (4.7)	16 (0.7)	65 (3.1)	1.6 (0.4, 2.8)
Pharyngitis	15 (0.7)	115 (5.4)	18 (0.8)	84 (4.0)	1.4 (0.1, 2.7)
Blood cholesterol increased	4 (0.2)	48 (2.3)	3 (0.1)	23 (1.1)	1.2 (0.4, 1.9)
Fatigue	52 (2.3)	87 (4.1)	59 (2.6)	60 (2.9)	1.2 (0.1, 2.3)
Headache	122 (5.3)	299 (14.1)	124 (5.4)	268 (12.9)	1.2 (-0.8, 3.3)
Injection site pruritus	0	46 (2.2)	0	24 (1.2)	1.0 (0.2, 1.8)
Abdominal pain upper	16 (0.7)	41 (1.9)	19 (0.8)	24 (1.2)	0.8 (0.0, 1.5)
Abdominal pain	17 (0.7)	45 (2.1)	26 (1.1)	30 (1.4)	0.7 (-0.1, 1.5)
Anxiety	8 (0.4)	72 (3.4)	14 (0.6)	60 (2.9)	0.5 (-0.5, 1.6)
Cellulitis	2 (0.09)	23 (1.1)	1 (0.04)	12 (0.6)	0.5 (-0.0, 1.1)
Myalgia	17 (0.7)	96 (4.5)	16 (0.7)	85 (4.1)	0.5 (-0.8, 1.7)
Pharyngitis streptococcal	7 (0.3)	43 (2.0)	1 (0.04)	31 (1.5)	0.5 (-0.3, 1.3)

Preferred Term	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Urethritis gonococcal	4 (0.2)	62 (2.9)	4 (0.2)	51 (2.5)	0.5 (-0.5, 1.5)
Urinary tract infection	2 (0.09)	30 (1.4)	3 (0.1)	20 (1.0)	0.5 (-0.2, 1.1)
Blood triglycerides increased	4 (0.2)	38 (1.8)	4 (0.2)	28 (1.3)	0.4 (-0.3, 1.2)
Dysuria	3 (0.1)	49 (2.3)	4 (0.2)	40 (1.9)	0.4 (-0.5, 1.3)
Furuncle	3 (0.1)	31 (1.5)	7 (0.3)	22 (1.1)	0.4 (-0.3, 1.1)
Genitourinary tract gonococcal infection	0	22 (1.0)	2 (0.09)	14 (0.7)	0.4 (-0.2, 0.9)
Hyperglycemia	2 (0.09)	37 (1.7)	4 (0.2)	29 (1.4)	0.4 (-0.4, 1.1)
Hypersensitivity	6 (0.3)	24 (1.1)	7 (0.3)	15 (0.7)	0.4 (-0.2, 1.0)
Influenza like illness	3 (0.1)	42 (2.0)	4 (0.2)	32 (1.5)	0.4 (-0.3, 1.2)
Musculoskeletal pain	2 (0.09)	35 (1.7)	5 (0.2)	27 (1.3)	0.4 (-0.4, 1.1)
Oropharyngeal gonococcal infection	3 (0.1)	36 (1.7)	2 (0.09)	28 (1.3)	0.4 (-0.4, 1.1)
Anogenital warts	6 (0.3)	38 (1.8)	4 (0.2)	32 (1.5)	0.3 (-0.5, 1.0)
Depression	10 (0.4)	71 (3.4)	11 (0.5)	63 (3.0)	0.3 (-0.7, 1.4)
Diarrhea	129 (5.7)	229 (10.8)	152 (6.7)	219 (10.5)	0.3 (-1.6, 2.2)
Genital herpes	8 (0.4)	32 (1.5)	2 (0.09)	26 (1.2)	0.3 (-0.4, 1.0)
Genitourinary chlamydia infection	2 (0.09)	29 (1.4)	1 (0.04)	22 (1.1)	0.3 (-0.3, 1.0)
Injection site anesthesia	0	25 (1.2)	0	18 (0.9)	0.3 (-0.3, 0.9)
Latent syphilis	1 (0.04)	65 (3.1)	1 (0.04)	58 (2.8)	0.3 (-0.7, 1.3)
Urethral discharge	2 (0.09)	24 (1.1)	1 (0.04)	18 (0.9)	0.3 (-0.3, 0.9)
Urticaria	2 (0.09)	29 (1.4)	6 (0.3)	22 (1.1)	0.3 (-0.3, 1.0)
Abnormal dreams	35 (1.5)	47 (2.2)	47 (2.1)	43 (2.1)	0.2 (-0.7, 1.0)
Cough	11 (0.5)	120 (5.7)	29 (1.3)	113 (5.4)	0.2 (-1.1, 1.6)
Gonorrhea	2 (0.09)	57 (2.7)	6 (0.3)	52 (2.5)	0.2 (-0.8, 1.2)
Ligament sprain	4 (0.2)	42 (2.0)	5 (0.2)	37 (1.8)	0.2 (-0.6, 1.0)
Pain	2 (0.09)	24 (1.1)	2 (0.09)	19 (0.9)	0.2 (-0.4, 0.8)
Rhinitis	8 (0.4)	34 (1.6)	7 (0.3)	29 (1.4)	0.2 (-0.5, 0.9)
Sinus congestion	3 (0.1)	31 (1.5)	7 (0.3)	26 (1.2)	0.2 (-0.5, 0.9)
Tension headache	5 (0.2)	23 (1.1)	6 (0.3)	19 (0.9)	0.2 (-0.4, 0.8)
Urethritis	6 (0.3)	60 (2.8)	5 (0.2)	55 (2.6)	0.2 (-0.8, 1.2)
Vomiting	14 (0.6)	48 (2.3)	36 (1.6)	42 (2.0)	0.2 (-0.6, 1.1)
Conjunctivitis	6 (0.3)	27 (1.3)	3 (0.1)	25 (1.2)	0.1 (-0.6, 0.7)
Dizziness	47 (2.1)	52 (2.5)	77 (3.4)	50 (2.4)	0.1 (-0.9, 1.0)
Food poisoning	8 (0.4)	48 (2.3)	9 (0.4)	46 (2.2)	0.1 (-0.8, 1.0)
Gastritis	4 (0.2)	36 (1.7)	3 (0.1)	33 (1.6)	0.1 (-0.7, 0.9)
Skin abrasion	5 (0.2)	32 (1.5)	2 (0.09)	29 (1.4)	0.1 (-0.6, 0.8)
Gastroenteritis	9 (0.4)	103 (4.9)	20 (0.9)	102 (4.9)	-0.0 (-1.3, 1.3)
Gastroesophageal reflux disease	6 (0.3)	24 (1.1)	4 (0.2)	23 (1.1)	0.0 (-0.6, 0.7)
Hordeolum	3 (0.1)	22 (1.0)	3 (0.1)	21 (1.0)	0.0 (-0.6, 0.6)
Hypoglycemia	4 (0.2)	29 (1.4)	3 (0.1)	29 (1.4)	-0.0 (-0.7, 0.7)
Hypophosphatasemia	4 (0.2)	22 (1.0)	7 (0.3)	22 (1.1)	-0.0 (-0.6, 0.6)
Oral herpes	8 (0.4)	35 (1.7)	1 (0.04)	34 (1.6)	0.0 (-0.7, 0.8)
Primary syphilis	0	23 (1.1)	1 (0.04)	22 (1.1)	0.0 (-0.6, 0.7)
Rhinitis allergic	4 (0.2)	41 (1.9)	8 (0.4)	40 (1.9)	0.0 (-0.8, 0.8)
Skin laceration	5 (0.2)	33 (1.6)	3 (0.1)	33 (1.6)	-0.0 (-0.8, 0.7)
Viral infection	5 (0.2)	72 (3.4)	7 (0.3)	71 (3.4)	-0.0 (-1.1, 1.1)
Aphthous ulcer	9 (0.4)	20 (0.9)	8 (0.4)	21 (1.0)	-0.1 (-0.7, 0.5)
Gastroenteritis viral	12 (0.5)	23 (1.1)	4 (0.2)	24 (1.2)	-0.1 (-0.7, 0.6)

Preferred Term	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Hemorrhoids	11 (0.5)	56 (2.6)	4 (0.2)	57 (2.7)	-0.1 (-1.1, 0.9)
Pain in extremity	9 (0.4)	47 (2.2)	7 (0.3)	49 (2.4)	-0.1 (-1.0, 0.8)
Sinusitis	4 (0.2)	47 (2.2)	6 (0.3)	48 (2.3)	-0.1 (-1.0, 0.8)
Bronchitis	3 (0.1)	30 (1.4)	5 (0.2)	34 (1.6)	-0.2 (-1.0, 0.5)
Chlamydial infection	7 (0.3)	66 (3.1)	7 (0.3)	69 (3.3)	-0.2 (-1.3, 0.9)
Contusion	4 (0.2)	24 (1.1)	4 (0.2)	27 (1.3)	-0.2 (-0.8, 0.5)
Dermatitis contact	4 (0.2)	26 (1.2)	3 (0.1)	29 (1.4)	-0.2 (-0.9, 0.5)
Nasal congestion	9 (0.4)	39 (1.8)	6 (0.3)	43 (2.1)	-0.2 (-1.1, 0.6)
Nasopharyngitis	78 (3.4)	344 (16.2)	59 (2.6)	343 (16.5)	-0.2 (-2.5, 2.0)
Nausea	79 (3.5)	79 (3.7)	138 (6.0)	81 (3.9)	-0.2 (-1.3, 1.0)
Rash	14 (0.6)	52 (2.5)	8 (0.4)	55 (2.6)	-0.2 (-1.1, 0.8)
Urethritis chlamydial	2 (0.09)	53 (2.5)	5 (0.2)	57 (2.7)	-0.2 (-1.2, 0.7)
Anal fissure	4 (0.2)	25 (1.2)	3 (0.1)	31 (1.5)	-0.3 (-1.0, 0.4)
Constipation	13 (0.6)	22 (1.0)	14 (0.6)	27 (1.3)	-0.3 (-0.9, 0.4)
Depressed mood	4 (0.2)	14 (0.7)	1 (0.04)	21 (1.0)	-0.3 (-0.9, 0.2)
Flatulence	22 (1.0)	17 (0.8)	32 (1.4)	22 (1.1)	-0.3 (-0.8, 0.3)
Folliculitis	5 (0.2)	29 (1.4)	0	34 (1.6)	-0.3 (-1.0, 0.5)
Influenza	13 (0.6)	73 (3.4)	11 (0.5)	77 (3.7)	-0.3 (-1.4, 0.9)
Insomnia	42 (1.8)	100 (4.7)	26 (1.1)	104 (5.0)	-0.3 (-1.6, 1.0)
Muscle strain	8 (0.4)	45 (2.1)	4 (0.2)	50 (2.4)	-0.3 (-1.2, 0.6)
Oropharyngeal pain	26 (1.1)	135 (6.4)	30 (1.3)	139 (6.7)	-0.3 (-1.8, 1.2)
Rhinorrhea	12 (0.5)	41 (1.9)	13 (0.6)	46 (2.2)	-0.3 (-1.1, 0.6)
Secondary syphilis	0	26 (1.2)	1 (0.04)	32 (1.5)	-0.3 (-1.0, 0.4)
Sinus arrhythmia	0	14 (0.7)	0	21 (1.0)	-0.3 (-0.9, 0.2)
Tonsillitis	10 (0.4)	54 (2.6)	8 (0.4)	60 (2.9)	-0.3 (-1.3, 0.7)
Acarodermatitis	1 (0.04)	36 (1.7)	7 (0.3)	43 (2.1)	-0.4 (-1.2, 0.5)
Arthralgia	14 (0.6)	78 (3.7)	21 (0.9)	84 (4.0)	-0.4 (-1.5, 0.8)
Lymphadenopathy	4 (0.2)	20 (0.9)	5 (0.2)	28 (1.3)	-0.4 (-1.0, 0.2)
Proctalgia	2 (0.09)	16 (0.8)	2 (0.09)	24 (1.2)	-0.4 (-1.0, 0.2)
Proctitis chlamydial	0	34 (1.6)	0	41 (2.0)	-0.4 (-1.2, 0.4)
Pruritus	11 (0.5)	20 (0.9)	18 (0.8)	28 (1.3)	-0.4 (-1.0, 0.2)
Viral upper respiratory tract infection	23 (1.0)	72 (3.4)	16 (0.7)	80 (3.8)	-0.4 (-1.6, 0.7)
Acne	8 (0.4)	34 (1.6)	13 (0.6)	43 (2.1)	-0.5 (-1.3, 0.4)
Blood glucose decreased	15 (0.7)	96 (4.5)	19 (0.8)	105 (5.0)	-0.5 (-1.8, 0.8)
Limb injury	6 (0.3)	13 (0.6)	5 (0.2)	23 (1.1)	-0.5 (-1.1, 0.1)
Proteinuria	1 (0.04)	12 (0.6)	0	23 (1.1)	-0.5 (-1.1, 0.0)
Seasonal allergy	9 (0.4)	29 (1.4)	5 (0.2)	38 (1.8)	-0.5 (-1.2, 0.3)
Dyspepsia	18 (0.8)	33 (1.6)	28 (1.2)	44 (2.1)	-0.6 (-1.4, 0.3)
Arthropod bite	6 (0.3)	14 (0.7)	7 (0.3)	29 (1.4)	-0.7 (-1.3, -0.1)
Aspartate aminotransferase increased	34 (1.5)	185 (8.7)	31 (1.4)	197 (9.5)	-0.7 (-2.5, 1.0)
Lipase increased	51 (2.2)	228 (10.8)	63 (2.8)	239 (11.5)	-0.7 (-2.6, 1.2)
Blood creatine phosphokinase increased	92 (4.0)	445 (21.0)	79 (3.5)	455 (21.9)	-0.8 (-3.3, 1.6)
Back pain	25 (1.1)	104 (4.9)	25 (1.1)	120 (5.8)	-0.9 (-2.2, 0.5)
Blood bilirubin increased	29 (1.3)	91 (4.3)	28 (1.2)	108 (5.2)	-0.9 (-2.2, 0.4)
Blood pressure increased	28 (1.2)	93 (4.4)	26 (1.1)	110 (5.3)	-0.9 (-2.2, 0.4)
Syphilis	5 (0.2)	196 (9.3)	7 (0.3)	211 (10.1)	-0.9 (-2.7, 0.9)
Proctitis gonococcal	6 (0.3)	214 (10.1)	8 (0.4)	232 (11.1)	-1.0 (-2.9, 0.8)
Toothache	6 (0.3)	38 (1.8)	10 (0.4)	59 (2.8)	-1.0 (-2.0, -0.1)

Preferred Term	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Blood phosphorus decreased	21 (0.9)	92 (4.3)	20 (0.9)	113 (5.4)	-1.1 (-2.4, 0.2)
Neutrophil count decreased	6 (0.3)	24 (1.1)	6 (0.3)	46 (2.2)	-1.1 (-1.9, -0.3)
Procedural pain	9 (0.4)	83 (3.9)	9 (0.4)	104 (5.0)	-1.1 (-2.3, 0.2)
Upper respiratory tract infection	49 (2.1)	234 (11.1)	39 (1.7)	252 (12.1)	-1.1 (-3.0, 0.9)
Weight decreased	0	18 (0.9)	3 (0.1)	40 (1.9)	-1.1 (-1.8, -0.4)
Amylase increased	59 (2.6)	135 (6.4)	54 (2.4)	158 (7.6)	-1.2 (-2.8, 0.3)
Abnormal loss of weight	2 (0.09)	34 (1.6)	2 (0.09)	60 (2.9)	-1.3 (-2.2, -0.4)
Anal chlamydia infection	10 (0.4)	256 (12.1)	9 (0.4)	292 (14.0)	-1.9 (-4.0, 0.1)
Alanine aminotransferase increased	32 (1.4)	159 (7.5)	33 (1.4)	198 (9.5)	-2.0 (-3.7, -0.3)
Blood creatinine increased	61 (2.7)	357 (16.9)	66 (2.9)	395 (19.0)	-2.1 (-4.4, 0.2)
Creatinine renal clearance decreased	689 (30.2)	1,438 (67.9)	699 (30.6)	1,525 (73.3)	-5.4 (-8.1, -2.6)

Source: adae.xpt; Software: R
Duration is median 29 days for Step 1 groups and median 457 days for Step 2 groups.
Treatment-emergent adverse events defined as any AE after the first dose of study drug and until 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively). For those with no injections, events after the first of 1 day after the date of discontinuation or 120 days after randomization were considered not treatment-emergent.
Coded as MedDRA preferred terms.
Recoding was performed as follows. Anogenital warts replaces: Papilloma viral infection. Gastroenteritis viral replaces: Gastrointestinal viral infection. Genital herpes replaces: Herpes simplex. Insomnia replaces: Initial insomnia.
Risk difference column shows difference (with 95% confidence interval) between step 2 groups.
Abbreviations: AE, adverse event; CAB, cabotegravir; CI, confidence interval; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 116. Adverse Events by System Organ Class and Preferred Term, Terms Occurring in at Least 1% of Any Arm, Safety Population, Trial HPTN 084

System Organ Class Preferred Term	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Blood and lymphatic system disorders (SOC)	17 (1.1)	71 (4.7)	12 (0.7)	61 (4.0)	0.7 (-0.8, 2.1)
Neutropenia	8 (0.5)	37 (2.4)	3 (0.2)	24 (1.6)	0.9 (-0.1, 1.9)
Cardiac disorders (SOC)	2 (0.1)	19 (1.3)	3 (0.2)	25 (1.6)	-0.4 (-1.2, 0.5)
Eye disorders (SOC)	13 (0.8)	53 (3.5)	9 (0.6)	39 (2.6)	0.9 (-0.3, 2.1)
Conjunctivitis allergic	5 (0.3)	35 (2.3)	2 (0.1)	24 (1.6)	0.7 (-0.3, 1.7)
Gastrointestinal disorders (SOC)	176 (10.9)	381 (25.1)	279 (17.3)	412 (27.2)	-2.1 (-5.2, 1.0)
Haemorrhoids	0	17 (1.1)	1 (0.06)	7 (0.5)	0.7 (0.0, 1.3)
Diarrhoea	47 (2.9)	59 (3.9)	71 (4.4)	53 (3.5)	0.4 (-1.0, 1.7)
Gastrooesophageal reflux disease	2 (0.1)	19 (1.3)	4 (0.2)	16 (1.1)	0.2 (-0.6, 1.0)
Constipation	2 (0.1)	17 (1.1)	5 (0.3)	17 (1.1)	-0.0 (-0.8, 0.7)
Abdominal pain lower	4 (0.2)	36 (2.4)	9 (0.6)	38 (2.5)	-0.1 (-1.2, 1.0)
Dyspepsia	7 (0.4)	66 (4.3)	19 (1.2)	67 (4.4)	-0.1 (-1.5, 1.4)
Toothache	4 (0.2)	23 (1.5)	5 (0.3)	25 (1.6)	-0.1 (-1.0, 0.8)
Abdominal pain	26 (1.6)	57 (3.8)	27 (1.7)	60 (4.0)	-0.2 (-1.6, 1.2)
Gastritis	11 (0.7)	73 (4.8)	12 (0.7)	76 (5.0)	-0.2 (-1.7, 1.3)
Vomiting	18 (1.1)	32 (2.1)	58 (3.6)	38 (2.5)	-0.4 (-1.5, 0.7)
Dental caries	4 (0.2)	33 (2.2)	6 (0.4)	45 (3.0)	-0.8 (-1.9, 0.3)

System Organ Class Preferred Term	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Nausea	49 (3.0)	33 (2.2)	116 (7.2)	56 (3.7)	-1.5 (-2.7, -0.3)
General disorders and administration site conditions (SOC)	59 (3.7)	625 (41.1)	71 (4.4)	253 (16.7)	24.5 (21.4, 27.6)
Injection site pain	4 (0.2)	520 (34.2)	2 (0.1)	145 (9.6)	24.7 (21.9, 27.5)
Injection site swelling	1 (0.06)	104 (6.8)	0	5 (0.3)	6.5 (5.2, 7.8)
Injection site nodule	0	80 (5.3)	1 (0.06)	4 (0.3)	5.0 (3.9, 6.2)
Injection site induration	0	70 (4.6)	0	4 (0.3)	4.3 (3.3, 5.4)
Injection site erythema	0	29 (1.9)	0	3 (0.2)	1.7 (1.0, 2.4)
Injection site pruritus	0	33 (2.2)	0	19 (1.3)	0.9 (-0.0, 1.8)
Pyrexia	3 (0.2)	19 (1.3)	5 (0.3)	16 (1.1)	0.2 (-0.6, 1.0)
Fatigue	25 (1.5)	16 (1.1)	29 (1.8)	17 (1.1)	-0.1 (-0.8, 0.7)
Influenza like illness	11 (0.7)	31 (2.0)	14 (0.9)	34 (2.2)	-0.2 (-1.2, 0.8)
Immune system disorders (SOC)	8 (0.5)	33 (2.2)	14 (0.9)	31 (2.0)	0.1 (-0.9, 1.1)
Seasonal allergy	7 (0.4)	21 (1.4)	7 (0.4)	22 (1.5)	-0.1 (-0.9, 0.8)
Infections and infestations (SOC)	305 (18.9)	964 (63.5)	325 (20.2)	960 (63.3)	0.1 (-3.3, 3.6)
Respiratory tract infection	11 (0.7)	49 (3.2)	9 (0.6)	29 (1.9)	1.3 (0.2, 2.4)
Vulvovaginitis trichomonal	1 (0.06)	126 (8.3)	4 (0.2)	106 (7.0)	1.3 (-0.6, 3.2)
Urinary tract infection	36 (2.2)	206 (13.6)	43 (2.7)	189 (12.5)	1.1 (-1.3, 3.5)
Body tinea	9 (0.6)	46 (3.0)	5 (0.3)	32 (2.1)	0.9 (-0.2, 2.0)
Tonsillitis	9 (0.6)	56 (3.7)	11 (0.7)	42 (2.8)	0.9 (-0.3, 2.2)
Folliculitis	6 (0.4)	22 (1.4)	4 (0.2)	11 (0.7)	0.7 (-0.0, 1.5)
Tinea versicolour	4 (0.2)	31 (2.0)	4 (0.2)	20 (1.3)	0.7 (-0.2, 1.6)
Gastroenteritis	10 (0.6)	89 (5.9)	24 (1.5)	80 (5.3)	0.6 (-1.0, 2.2)
Trichomoniasis	0	19 (1.3)	0	12 (0.8)	0.5 (-0.3, 1.2)
Pharyngitis	5 (0.3)	23 (1.5)	5 (0.3)	17 (1.1)	0.4 (-0.4, 1.2)
Rhinitis	3 (0.2)	27 (1.8)	5 (0.3)	21 (1.4)	0.4 (-0.5, 1.3)
Viral upper respiratory tract infection	11 (0.7)	41 (2.7)	15 (0.9)	35 (2.3)	0.4 (-0.7, 1.5)
Gonorrhoea	2 (0.1)	20 (1.3)	2 (0.1)	15 (1.0)	0.3 (-0.4, 1.1)
Sinusitis	1 (0.06)	16 (1.1)	2 (0.1)	12 (0.8)	0.3 (-0.4, 0.9)
Vaginal infection	5 (0.3)	27 (1.8)	4 (0.2)	23 (1.5)	0.3 (-0.6, 1.2)
Influenza	14 (0.9)	44 (2.9)	10 (0.6)	41 (2.7)	0.2 (-1.0, 1.4)
Syphilis	0	29 (1.9)	0	26 (1.7)	0.2 (-0.8, 1.1)
Gastroenteritis bacterial	3 (0.2)	27 (1.8)	4 (0.2)	26 (1.7)	0.1 (-0.9, 1.0)
Pelvic inflammatory disease	6 (0.4)	47 (3.1)	6 (0.4)	46 (3.0)	0.1 (-1.2, 1.3)
Bacterial vaginosis	2 (0.1)	36 (2.4)	1 (0.06)	37 (2.4)	-0.1 (-1.2, 1.0)
Genitourinary tract gonococcal infection	0	68 (4.5)	0	69 (4.6)	-0.1 (-1.6, 1.4)
Gonococcal infection	0	38 (2.5)	2 (0.1)	40 (2.6)	-0.1 (-1.3, 1.0)
Genitourinary chlamydia infection	3 (0.2)	144 (9.5)	2 (0.1)	146 (9.6)	-0.2 (-2.2, 1.9)
Conjunctivitis	4 (0.2)	26 (1.7)	9 (0.6)	30 (2.0)	-0.3 (-1.2, 0.7)
Sexually transmitted disease	2 (0.1)	34 (2.2)	4 (0.2)	39 (2.6)	-0.3 (-1.4, 0.8)
Fungal skin infection	8 (0.5)	33 (2.2)	3 (0.2)	39 (2.6)	-0.4 (-1.5, 0.7)
Subcutaneous abscess	2 (0.1)	16 (1.1)	1 (0.06)	25 (1.6)	-0.6 (-1.4, 0.2)
Nasopharyngitis	16 (1.0)	71 (4.7)	20 (1.2)	82 (5.4)	-0.7 (-2.3, 0.8)
Malaria	12 (0.7)	44 (2.9)	9 (0.6)	58 (3.8)	-0.9 (-2.2, 0.4)

System Organ Class Preferred Term	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Vulvovaginal candidiasis	25 (1.5)	118 (7.8)	33 (2.0)	139 (9.2)	-1.4 (-3.4, 0.6)
Upper respiratory tract infection	82 (5.1)	225 (14.8)	73 (4.5)	255 (16.8)	-2.0 (-4.6, 0.6)
Chlamydial infection	1 (0.06)	109 (7.2)	5 (0.3)	140 (9.2)	-2.1 (-4.0, -0.1)
Injury, poisoning and procedural complications (SOC)	26 (1.6)	128 (8.4)	25 (1.6)	146 (9.6)	-1.2 (-3.2, 0.8)
Muscle strain	2 (0.1)	16 (1.1)	0	13 (0.9)	0.2 (-0.5, 0.9)
Procedural pain	0	18 (1.2)	1 (0.06)	18 (1.2)	-0.0 (-0.8, 0.8)
Soft tissue injury	2 (0.1)	24 (1.6)	4 (0.2)	31 (2.0)	-0.5 (-1.4, 0.5)
Investigations (SOC)	1,031 (63.9)	1,422 (93.6)	1,056 (65.6)	1,401 (92.4)	1.2 (-0.6, 3.0)
Blood glucose increased	199 (12.3)	504 (33.2)	129 (8.0)	401 (26.5)	6.7 (3.5, 10.0)
Lipase increased	53 (3.3)	180 (11.8)	63 (3.9)	140 (9.2)	2.6 (0.4, 4.8)
Aspartate aminotransferase increased	27 (1.7)	196 (12.9)	20 (1.2)	170 (11.2)	1.7 (-0.6, 4.0)
Blood calcium increased	18 (1.1)	92 (6.1)	10 (0.6)	70 (4.6)	1.4 (-0.2, 3.0)
Blood creatinine increased	98 (6.1)	321 (21.1)	90 (5.6)	310 (20.4)	0.7 (-2.2, 3.6)
Low density lipoprotein increased	2 (0.1)	54 (3.6)	1 (0.06)	45 (3.0)	0.6 (-0.7, 1.9)
Blood cholesterol increased	3 (0.2)	34 (2.2)	0	27 (1.8)	0.5 (-0.5, 1.5)
Platelet count decreased	13 (0.8)	38 (2.5)	8 (0.5)	31 (2.0)	0.5 (-0.6, 1.5)
Blood pressure increased	11 (0.7)	66 (4.3)	13 (0.8)	60 (4.0)	0.4 (-1.0, 1.8)
Alanine aminotransferase increased	28 (1.7)	219 (14.4)	29 (1.8)	217 (14.3)	0.1 (-2.4, 2.6)
Blood triglycerides increased	1 (0.06)	29 (1.9)	0	27 (1.8)	0.1 (-0.8, 1.1)
Neutrophil count decreased	14 (0.9)	60 (3.9)	21 (1.3)	59 (3.9)	0.1 (-1.3, 1.4)
White blood cell count decreased	3 (0.2)	21 (1.4)	8 (0.5)	27 (1.8)	-0.4 (-1.3, 0.5)
Amylase increased	194 (12.0)	512 (33.7)	190 (11.8)	518 (34.2)	-0.5 (-3.8, 2.9)
Blood bilirubin increased	9 (0.6)	68 (4.5)	10 (0.6)	76 (5.0)	-0.5 (-2.0, 1.0)
Blood glucose decreased	101 (6.3)	378 (24.9)	109 (6.8)	386 (25.5)	-0.6 (-3.7, 2.5)
Hemoglobin decreased	21 (1.3)	63 (4.1)	22 (1.4)	73 (4.8)	-0.7 (-2.1, 0.8)
Blood calcium decreased	14 (0.9)	69 (4.5)	18 (1.1)	87 (5.7)	-1.2 (-2.8, 0.4)
Blood alkaline phosphatase increased	10 (0.6)	47 (3.1)	10 (0.6)	67 (4.4)	-1.3 (-2.7, 0.0)
Blood creatine phosphokinase increased	49 (3.0)	206 (13.6)	48 (3.0)	229 (15.1)	-1.5 (-4.0, 0.9)
Blood phosphorus decreased	72 (4.5)	246 (16.2)	113 (7.0)	274 (18.1)	-1.9 (-4.6, 0.8)
Creatinine renal clearance decreased	627 (38.8)	1,018 (67.0)	652 (40.5)	1,062 (70.1)	-3.0 (-6.3, 0.3)

System Organ Class Preferred Term	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Metabolism and nutrition disorders (SOC)	99 (6.1)	271 (17.8)	113 (7.0)	285 (18.8)	-1.0 (-3.7, 1.8)
Hyperglycemia	39 (2.4)	119 (7.8)	30 (1.9)	95 (6.3)	1.6 (-0.3, 3.4)
Hypoglycemia	13 (0.8)	46 (3.0)	20 (1.2)	45 (3.0)	0.1 (-1.2, 1.3)
Hypophosphatemia	8 (0.5)	18 (1.2)	7 (0.4)	16 (1.1)	0.1 (-0.6, 0.9)
Increased appetite	17 (1.1)	2 (0.1)	14 (0.9)	4 (0.3)	-0.1 (-0.4, 0.2)
Decreased appetite	20 (1.2)	41 (2.7)	41 (2.5)	57 (3.8)	-1.1 (-2.3, 0.2)
Abnormal loss of weight	1 (0.06)	79 (5.2)	3 (0.2)	102 (6.7)	-1.5 (-3.2, 0.2)
Musculoskeletal and connective tissue disorders (SOC)	53 (3.3)	280 (18.4)	49 (3.0)	240 (15.8)	2.6 (-0.1, 5.3)
Back pain	12 (0.7)	127 (8.4)	23 (1.4)	115 (7.6)	0.8 (-1.2, 2.7)
Myalgia	12 (0.7)	43 (2.8)	6 (0.4)	31 (2.0)	0.8 (-0.3, 1.9)
Musculoskeletal pain	5 (0.3)	44 (2.9)	3 (0.2)	36 (2.4)	0.5 (-0.6, 1.7)
Pain in extremity	5 (0.3)	26 (1.7)	2 (0.1)	23 (1.5)	0.2 (-0.7, 1.1)
Musculoskeletal chest pain	7 (0.4)	27 (1.8)	4 (0.2)	27 (1.8)	-0.0 (-0.9, 0.9)
Arthralgia	12 (0.7)	38 (2.5)	4 (0.2)	44 (2.9)	-0.4 (-1.6, 0.8)
Nervous system disorders (SOC)	234 (14.5)	388 (25.5)	262 (16.3)	367 (24.2)	1.3 (-1.7, 4.4)
Headache	137 (8.5)	285 (18.8)	170 (10.6)	265 (17.5)	1.3 (-1.5, 4.0)
Somnolence	31 (1.9)	7 (0.5)	27 (1.7)	5 (0.3)	0.1 (-0.3, 0.6)
Tension headache	17 (1.1)	65 (4.3)	19 (1.2)	70 (4.6)	-0.3 (-1.8, 1.1)
Paraesthesia	3 (0.2)	17 (1.1)	1 (0.06)	29 (1.9)	-0.8 (-1.7, 0.1)
Dizziness	65 (4.0)	36 (2.4)	77 (4.8)	52 (3.4)	-1.1 (-2.3, 0.1)
Psychiatric disorders (SOC)	27 (1.7)	58 (3.8)	23 (1.4)	55 (3.6)	0.2 (-1.2, 1.5)
Insomnia	15 (0.9)	22 (1.4)	15 (0.9)	20 (1.3)	0.1 (-0.7, 1.0)
Renal and urinary disorders (SOC)	7 (0.4)	56 (3.7)	11 (0.7)	55 (3.6)	0.1 (-1.3, 1.4)
Proteinuria	5 (0.3)	48 (3.2)	11 (0.7)	48 (3.2)	-0.0 (-1.3, 1.2)
Reproductive system and breast disorders (SOC)	154 (9.5)	463 (30.5)	145 (9.0)	442 (29.2)	1.3 (-1.9, 4.6)
Vaginal discharge	17 (1.1)	81 (5.3)	15 (0.9)	62 (4.1)	1.2 (-0.3, 2.7)
Metrorrhagia	35 (2.2)	94 (6.2)	23 (1.4)	85 (5.6)	0.6 (-1.1, 2.3)
Dysfunctional uterine bleeding	41 (2.5)	139 (9.2)	44 (2.7)	136 (9.0)	0.2 (-1.9, 2.2)
Vaginal hemorrhage	7 (0.4)	16 (1.1)	7 (0.4)	13 (0.9)	0.2 (-0.5, 0.9)
Amenorrhea	6 (0.4)	59 (3.9)	9 (0.6)	58 (3.8)	0.1 (-1.3, 1.4)
Menometrorrhagia	6 (0.4)	20 (1.3)	4 (0.2)	21 (1.4)	-0.1 (-0.9, 0.8)
Vulvovaginal pruritus	8 (0.5)	28 (1.8)	6 (0.4)	31 (2.0)	-0.2 (-1.2, 0.8)
Menorrhagia	22 (1.4)	83 (5.5)	21 (1.3)	87 (5.7)	-0.3 (-1.9, 1.4)
Dysmenorrhea	11 (0.7)	46 (3.0)	14 (0.9)	62 (4.1)	-1.1 (-2.4, 0.3)
Respiratory, thoracic and mediastinal disorders (SOC)	24 (1.5)	105 (6.9)	29 (1.8)	88 (5.8)	1.1 (-0.6, 2.8)
Nasal congestion	2 (0.1)	19 (1.3)	5 (0.3)	12 (0.8)	0.5 (-0.3, 1.2)
Cough	7 (0.4)	29 (1.9)	5 (0.3)	25 (1.6)	0.3 (-0.7, 1.2)
Rhinitis allergic	6 (0.4)	22 (1.4)	2 (0.1)	17 (1.1)	0.3 (-0.5, 1.1)

System Organ Class Preferred Term	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Skin and subcutaneous tissue disorders (SOC)	57 (3.5)	206 (13.6)	80 (5.0)	167 (11.0)	2.5 (0.2, 4.9)
Dermatitis	4 (0.2)	26 (1.7)	3 (0.2)	13 (0.9)	0.9 (0.1, 1.7)
Dermatitis allergic	6 (0.4)	40 (2.6)	8 (0.5)	34 (2.2)	0.4 (-0.7, 1.5)
Pruritus	9 (0.6)	32 (2.1)	23 (1.4)	27 (1.8)	0.3 (-0.7, 1.3)
Rash	9 (0.6)	26 (1.7)	12 (0.7)	22 (1.5)	0.3 (-0.6, 1.1)
Acne	2 (0.1)	17 (1.1)	6 (0.4)	16 (1.1)	0.1 (-0.7, 0.8)
Vascular disorders (SOC)	8 (0.5)	52 (3.4)	4 (0.2)	44 (2.9)	0.5 (-0.7, 1.8)
Hypertension	5 (0.3)	33 (2.2)	2 (0.1)	35 (2.3)	-0.1 (-1.2, 0.9)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE with an onset date on or after the start of treatment and before 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively).
Duration is median 29 days for Step 1 groups and median 452 days for Step 2 groups.
Recoding was performed as follows. Anogenital warts replaces: Papilloma viral infection. Gastroenteritis viral replaces: Gastrointestinal viral infection. Genital herpes replaces: Herpes simplex. Insomnia replaces: Initial insomnia.
Risk difference column shows difference (with 95% confidence interval) between step 2 groups.
Abbreviations: CAB, cabotegravir; CI, confidence interval; SOC, system organ class; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

17.4. Adverse Events of Special Interest, HPTN 083 and HPTN 084

Customized grouped queries were developed and conducted to explore AESIs. The completed analyses are presented in Tables 117 and 118. Please see Section 7.6.3 for an in-depth discussion of the AESIs.

Table 117. Adverse Events of Special Interest Grouped Queries, Safety Population, Trial HPTN 083

Grouped Query Preferred Term	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Pyrexia (GQ)	23 (1.0)	275 (13.0)	24 (1.1)	136 (6.5)	6.5 (4.7, 8.2)
Pyrexia	20 (0.9)	221 (10.4)	17 (0.7)	100 (4.8)	5.6 (4.0, 7.2)
Chills	2 (0.09)	21 (1.0)	2 (0.09)	6 (0.3)	0.7 (0.2, 1.2)
Influenza like illness	3 (0.1)	42 (2.0)	4 (0.2)	32 (1.5)	0.4 (-0.3, 1.2)
Feeling hot	0	2 (0.09)	1 (0.04)	0	0.1 (-0.0, 0.2)
Systemic injection site reactions (GQ)	22 (1.0)	262 (12.4)	23 (1.0)	136 (6.5)	5.8 (4.1, 7.6)
Pyrexia	20 (0.9)	221 (10.4)	17 (0.7)	100 (4.8)	5.6 (4.0, 7.2)
Musculoskeletal pain	2 (0.09)	35 (1.7)	5 (0.2)	27 (1.3)	0.4 (-0.4, 1.1)
Sciatica	0	8 (0.4)	0	8 (0.4)	-0.0 (-0.4, 0.4)
Hypotension	0	0	1 (0.04)	3 (0.1)	-0.1 (-0.3, 0.0)
Fatigue (GQ)	61 (2.7)	143 (6.8)	70 (3.1)	87 (4.2)	2.6 (1.2, 3.9)
Malaise	4 (0.2)	54 (2.6)	6 (0.3)	17 (0.8)	1.7 (1.0, 2.5)
Fatigue	52 (2.3)	87 (4.1)	59 (2.6)	60 (2.9)	1.2 (0.1, 2.3)
Asthenia	5 (0.2)	11 (0.5)	5 (0.2)	12 (0.6)	-0.1 (-0.5, 0.4)

Grouped Query Preferred Term	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Anxiety disorder (GQ)	9 (0.4)	88 (4.2)	17 (0.7)	71 (3.4)	0.7 (-0.4, 1.9)
Anxiety	8 (0.4)	72 (3.4)	14 (0.6)	60 (2.9)	0.5 (-0.5, 1.6)
Stress	1 (0.04)	10 (0.5)	1 (0.04)	6 (0.3)	0.2 (-0.2, 0.6)
Acute stress disorder	0	1 (0.05)	1 (0.04)	0	0.0 (-0.0, 0.1)
Anxiety disorder	0	3 (0.1)	0	3 (0.1)	-0.0 (-0.2, 0.2)
Panic disorder	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Panic attack	0	3 (0.1)	1 (0.04)	6 (0.3)	-0.1 (-0.4, 0.1)
Mood disorder (GQ)	24 (1.1)	118 (5.6)	21 (0.9)	102 (4.9)	0.7 (-0.7, 2.0)
Major depression	0	11 (0.5)	2 (0.09)	3 (0.1)	0.4 (0.0, 0.7)
Depression	10 (0.4)	71 (3.4)	11 (0.5)	63 (3.0)	0.3 (-0.7, 1.4)
Irritability	5 (0.2)	6 (0.3)	1 (0.04)	2 (0.1)	0.2 (-0.1, 0.5)
Mood swings	1 (0.04)	4 (0.2)	3 (0.1)	2 (0.1)	0.1 (-0.1, 0.3)
Affect lability	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Affective disorder	1 (0.04)	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Depression suicidal	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Intentional self-injury	1 (0.04)	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Mood altered	1 (0.04)	1 (0.05)	0	2 (0.1)	-0.0 (-0.2, 0.1)
Suicidal ideation	2 (0.09)	14 (0.7)	2 (0.09)	14 (0.7)	-0.0 (-0.5, 0.5)
Suicide attempt	2 (0.09)	6 (0.3)	1 (0.04)	9 (0.4)	-0.1 (-0.5, 0.2)
Depressed mood	4 (0.2)	14 (0.7)	1 (0.04)	21 (1.0)	-0.3 (-0.9, 0.2)
HSR (GQ)	24 (1.1)	112 (5.3)	18 (0.8)	96 (4.6)	0.7 (-0.6, 2.0)
Urticaria	2 (0.09)	29 (1.4)	6 (0.3)	22 (1.1)	0.3 (-0.3, 1.0)
Arthritis	0	4 (0.2)	0	2 (0.1)	0.1 (-0.1, 0.3)
Conjunctivitis	6 (0.3)	27 (1.3)	3 (0.1)	25 (1.2)	0.1 (-0.6, 0.7)
Mouth ulceration	3 (0.1)	6 (0.3)	0	3 (0.1)	0.1 (-0.1, 0.4)
Stomatitis	0	3 (0.1)	0	1 (0.05)	0.1 (-0.1, 0.3)
Drug eruption	1 (0.04)	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Drug hypersensitivity	3 (0.1)	5 (0.2)	1 (0.04)	4 (0.2)	0.0 (-0.2, 0.3)
Ear swelling	0	0	1 (0.04)	0	0 (0, 0)
Eosinophilia	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Eye swelling	1 (0.04)	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Eyelid oedema	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Gingival swelling	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Glossitis	1 (0.04)	2 (0.09)	0	1 (0.05)	0.0 (-0.1, 0.2)
Hypersensitivity	6 (0.3)	24 (1.1)	7 (0.3)	15 (0.7)	0.4 (-0.2, 1.0)
Joint swelling	0	4 (0.2)	0	3 (0.1)	0.0 (-0.2, 0.3)
Lip swelling	0	2 (0.09)	0	2 (0.1)	-0.0 (-0.2, 0.2)
Myositis	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Stevens-Johnson syndrome	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Swelling face	1 (0.04)	4 (0.2)	1 (0.04)	3 (0.1)	0.0 (-0.2, 0.3)
Swelling of eyelid	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Periorbital swelling	0	0	0	2 (0.1)	-0.1 (-0.2, 0.0)
Pruritus allergic	1 (0.04)	0	0	2 (0.1)	-0.1 (-0.2, 0.0)
Peripheral swelling	0	2 (0.09)	0	7 (0.3)	-0.2 (-0.5, 0.0)
Adjustment disorder (GQ)	1 (0.04)	6 (0.3)	2 (0.09)	8 (0.4)	-0.1 (-0.5, 0.2)
Adjustment disorder with depressed mood	1 (0.04)	4 (0.2)	1 (0.04)	4 (0.2)	-0.0 (-0.3, 0.3)
Adjustment disorder	0	2 (0.09)	1 (0.04)	4 (0.2)	-0.1 (-0.3, 0.1)

Grouped Query Preferred Term	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Musculoskeletal pain (GQ)	87 (3.8)	401 (18.9)	84 (3.7)	396 (19.0)	-0.1 (-2.5, 2.3)
Myalgia	17 (0.7)	96 (4.5)	16 (0.7)	85 (4.1)	0.5 (-0.8, 1.7)
Musculoskeletal pain	2 (0.09)	35 (1.7)	5 (0.2)	27 (1.3)	0.4 (-0.4, 1.1)
Bone pain	0	5 (0.2)	0	0	0.2 (0.0, 0.4)
Plantar fasciitis	1 (0.04)	10 (0.5)	1 (0.04)	6 (0.3)	0.2 (-0.2, 0.6)
Groin pain	1 (0.04)	4 (0.2)	0	2 (0.1)	0.1 (-0.1, 0.3)
Musculoskeletal chest pain	1 (0.04)	13 (0.6)	2 (0.09)	10 (0.5)	0.1 (-0.3, 0.6)
Musculoskeletal discomfort	0	2 (0.09)	0	0	0.1 (-0.0, 0.2)
Spinal pain	0	3 (0.1)	0	0	0.1 (-0.0, 0.3)
Bursitis	0	2 (0.09)	0	2 (0.1)	-0.0 (-0.2, 0.2)
Chondritis	1 (0.04)	0	0	0	0 (0, 0)
Costochondritis	0	3 (0.1)	0	3 (0.1)	-0.0 (-0.2, 0.2)
Enthesopathy	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Facet joint syndrome	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Intervertebral disc degeneration	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Intervertebral disc disorder	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Intervertebral disc displacement	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Intervertebral disc protrusion	0	7 (0.3)	0	6 (0.3)	0.0 (-0.3, 0.4)
Joint effusion	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Joint swelling	0	4 (0.2)	0	3 (0.1)	0.0 (-0.2, 0.3)
Limb discomfort	0	2 (0.09)	0	1 (0.05)	0.0 (-0.1, 0.2)
Metatarsalgia	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Muscle discomfort	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Muscle tightness	1 (0.04)	2 (0.09)	0	2 (0.1)	-0.0 (-0.2, 0.2)
Myositis	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Neck pain	2 (0.09)	16 (0.8)	4 (0.2)	15 (0.7)	0.0 (-0.5, 0.6)
Osteoarthritis	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Osteochondritis	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Patellofemoral pain syndrome	1 (0.04)	0	0	0	0 (0, 0)
Periarthritis	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Rotator cuff syndrome	0	2 (0.09)	0	1 (0.05)	0.0 (-0.1, 0.2)
Spinal osteoarthritis	0	2 (0.09)	0	1 (0.05)	0.0 (-0.1, 0.2)
Spinal stenosis	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Temporomandibular joint syndrome	0	1 (0.05)	1 (0.04)	1 (0.05)	-0.0 (-0.1, 0.1)
Tendon disorder	1 (0.04)	0	0	0	0 (0, 0)
Tendon pain	1 (0.04)	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Tendonitis	3 (0.1)	7 (0.3)	1 (0.04)	6 (0.3)	0.0 (-0.3, 0.4)
Tenosynovitis stenosans	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Torticollis	0	3 (0.1)	0	2 (0.1)	0.0 (-0.2, 0.3)
Joint stiffness	0	0	0	2 (0.1)	-0.1 (-0.2, 0.0)
Medial tibial stress syndrome	0	0	0	2 (0.1)	-0.1 (-0.2, 0.0)
Muscle spasms	3 (0.1)	13 (0.6)	3 (0.1)	15 (0.7)	-0.1 (-0.6, 0.4)
Musculoskeletal stiffness	2 (0.09)	5 (0.2)	0	8 (0.4)	-0.1 (-0.5, 0.2)
Pain in extremity	9 (0.4)	47 (2.2)	7 (0.3)	49 (2.4)	-0.1 (-1.0, 0.8)
Pain in jaw	1 (0.04)	4 (0.2)	1 (0.04)	7 (0.3)	-0.1 (-0.5, 0.2)

Grouped Query Preferred Term	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
Rhabdomyolysis	1 (0.04)	5 (0.2)	0	8 (0.4)	-0.1 (-0.5, 0.2)
Muscle strain	8 (0.4)	45 (2.1)	4 (0.2)	50 (2.4)	-0.3 (-1.2, 0.6)
Arthralgia	14 (0.6)	78 (3.7)	21 (0.9)	84 (4.0)	-0.4 (-1.5, 0.8)
Back pain	25 (1.1)	104 (4.9)	25 (1.1)	120 (5.8)	-0.9 (-2.2, 0.5)
Rash (GQ)	41 (1.8)	164 (7.7)	44 (1.9)	169 (8.1)	-0.4 (-2.0, 1.3)
Rash macular	1 (0.04)	12 (0.6)	1 (0.04)	2 (0.1)	0.5 (0.1, 0.8)
Dermatitis	3 (0.1)	17 (0.8)	1 (0.04)	11 (0.5)	0.3 (-0.2, 0.8)
Dermatitis allergic	1 (0.04)	14 (0.7)	4 (0.2)	11 (0.5)	0.1 (-0.3, 0.6)
Dermatitis papillaris capillitii	0	2 (0.09)	0	1 (0.05)	0.0 (-0.1, 0.2)
Drug eruption	1 (0.04)	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Erythema	3 (0.1)	11 (0.5)	1 (0.04)	10 (0.5)	0.0 (-0.4, 0.5)
Exfoliative rash	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Miliaria	0	2 (0.09)	1 (0.04)	1 (0.05)	0.0 (-0.1, 0.2)
Palmar erythema	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Penile rash	0	1 (0.05)	0	2 (0.1)	-0.0 (-0.2, 0.1)
Rash erythematous	1 (0.04)	4 (0.2)	0	3 (0.1)	0.0 (-0.2, 0.3)
Rash follicular	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Rash morbilliform	1 (0.04)	0	0	0	0 (0, 0)
Scrotal dermatitis	0	1 (0.05)	1 (0.04)	0	0.0 (-0.0, 0.1)
Skin reaction	0	0	1 (0.04)	0	0 (0, 0)
Solar dermatitis	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Vessel puncture site rash	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Viral rash	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Dermatitis atopic	1 (0.04)	4 (0.2)	0	7 (0.3)	-0.1 (-0.5, 0.2)
Genital rash	0	1 (0.05)	0	3 (0.1)	-0.1 (-0.3, 0.1)
Perioral dermatitis	0	0	0	2 (0.1)	-0.1 (-0.2, 0.0)
Rash pruritic	2 (0.09)	4 (0.2)	3 (0.1)	6 (0.3)	-0.1 (-0.4, 0.2)
Rash vesicular	0	1 (0.05)	1 (0.04)	3 (0.1)	-0.1 (-0.3, 0.1)
Dermatitis contact	4 (0.2)	26 (1.2)	3 (0.1)	29 (1.4)	-0.2 (-0.9, 0.5)
Rash	14 (0.6)	52 (2.5)	8 (0.4)	55 (2.6)	-0.2 (-1.1, 0.8)
Rash maculo-papular	0	4 (0.2)	0	8 (0.4)	-0.2 (-0.5, 0.1)
Rash papular	1 (0.04)	7 (0.3)	3 (0.1)	13 (0.6)	-0.3 (-0.7, 0.1)
Pruritus	11 (0.5)	20 (0.9)	18 (0.8)	28 (1.3)	-0.4 (-1.0, 0.2)
Sleep disorder (GQ)	60 (2.6)	116 (5.5)	51 (2.2)	134 (6.4)	-1.0 (-2.4, 0.5)
Circadian rhythm sleep disorder	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Poor quality sleep	1 (0.04)	4 (0.2)	1 (0.04)	4 (0.2)	-0.0 (-0.3, 0.3)
Sleep deficit	0	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Sleep disorder	0	2 (0.09)	4 (0.2)	4 (0.2)	-0.1 (-0.3, 0.1)
Somnolence	11 (0.5)	7 (0.3)	17 (0.7)	8 (0.4)	-0.1 (-0.4, 0.3)
Initial insomnia	1 (0.04)	1 (0.05)	0	6 (0.3)	-0.2 (-0.5, 0.0)
Nightmare	6 (0.3)	5 (0.2)	5 (0.2)	9 (0.4)	-0.2 (-0.5, 0.2)
Insomnia	42 (1.8)	100 (4.7)	26 (1.1)	104 (5.0)	-0.3 (-1.6, 1.0)

Grouped Query Preferred Term	CAB Step 1 N=2,281 n (%)	CAB Step 2 N=2,117 n (%)	TDF/FTC Step 1 N=2,285 n (%)	TDF/FTC Step 2 N=2,081 n (%)	Risk Difference (95% CI)
STI (GQ)	51 (2.2)	749 (35.4)	53 (2.3)	788 (37.9)	-2.5 (-5.4, 0.4)
Urethritis gonococcal	4 (0.2)	62 (2.9)	4 (0.2)	51 (2.5)	0.5 (-0.5, 1.5)
Genitourinary tract gonococcal infection	0	22 (1.0)	2 (0.09)	14 (0.7)	0.4 (-0.2, 0.9)
Oropharyngeal gonococcal infection	3 (0.1)	36 (1.7)	2 (0.09)	28 (1.3)	0.4 (-0.4, 1.1)
Anogenital warts	6 (0.3)	38 (1.8)	4 (0.2)	32 (1.5)	0.3 (-0.5, 1.0)
Genital herpes	8 (0.4)	32 (1.5)	2 (0.09)	26 (1.2)	0.3 (-0.4, 1.0)
Genitourinary chlamydia infection	2 (0.09)	29 (1.4)	1 (0.04)	22 (1.1)	0.3 (-0.3, 1.0)
Latent syphilis	1 (0.04)	65 (3.1)	1 (0.04)	58 (2.8)	0.3 (-0.7, 1.3)
Gonorrhea	2 (0.09)	57 (2.7)	6 (0.3)	52 (2.5)	0.2 (-0.8, 1.2)
Acute hepatitis C	1 (0.04)	7 (0.3)	0	5 (0.2)	0.1 (-0.2, 0.4)
Gonococcal infection	2 (0.09)	4 (0.2)	0	2 (0.1)	0.1 (-0.1, 0.3)
Pharyngeal chlamydia infection	0	11 (0.5)	1 (0.04)	8 (0.4)	0.1 (-0.3, 0.5)
Proctitis herpes	0	4 (0.2)	1 (0.04)	1 (0.05)	0.1 (-0.1, 0.3)
Anorectal human papilloma virus infection	0	10 (0.5)	3 (0.1)	9 (0.4)	0.0 (-0.4, 0.4)
Arthritis gonococcal	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Cervicitis human papilloma virus	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Chancroid	0	2 (0.09)	1 (0.04)	1 (0.05)	0.0 (-0.1, 0.2)
Eye infection gonococcal	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Hepatitis syphilitic	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Mycoplasma genitalium infection	0	0	0	1 (0.05)	-0.0 (-0.1, 0.0)
Primary syphilis	0	23 (1.1)	1 (0.04)	22 (1.1)	0.0 (-0.6, 0.7)
Syphilis anal	0	1 (0.05)	0	0	0.0 (-0.0, 0.1)
Syphilis genital	1 (0.04)	1 (0.05)	0	1 (0.05)	-0.0 (-0.1, 0.1)
Genital herpes simplex	1 (0.04)	13 (0.6)	1 (0.04)	14 (0.7)	-0.1 (-0.5, 0.4)
Lymphogranuloma venereum	0	4 (0.2)	1 (0.04)	5 (0.2)	-0.1 (-0.3, 0.2)
Molluscum contagiosum	0	2 (0.09)	1 (0.04)	5 (0.2)	-0.1 (-0.4, 0.1)
Urethritis chlamydial	2 (0.09)	53 (2.5)	5 (0.2)	57 (2.7)	-0.2 (-1.2, 0.7)
Secondary syphilis	0	26 (1.2)	1 (0.04)	32 (1.5)	-0.3 (-1.0, 0.4)
Proctitis chlamydial	0	34 (1.6)	0	41 (2.0)	-0.4 (-1.2, 0.4)
Syphilis	5 (0.2)	196 (9.3)	7 (0.3)	211 (10.1)	-0.9 (-2.7, 0.9)
Proctitis gonococcal	6 (0.3)	214 (10.1)	8 (0.4)	232 (11.1)	-1.0 (-2.9, 0.8)
Anal chlamydia infection	10 (0.4)	256 (12.1)	9 (0.4)	292 (14.0)	-1.9 (-4.0, 0.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE after the first dose of study drug and until 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively). For those with no injections, events after the first of 1 day after the date of discontinuation or 120 days after randomization were considered not treatment-emergent.
Duration is median 29 days for Step 1 groups and median 457 days for Step 2 groups.
Risk difference column shows difference (with 95% confidence interval) between step 2 groups.
Abbreviations: CAB, cabotegravir; CI, confidence interval; GQ, grouped query; HSR, hypersensitivity reaction; N, number of subjects in treatment arm; n, number of subjects with adverse event; STI, sexually transmitted infection; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 118. Adverse Events of Special Interest Grouped Queries, Safety Population, Trial HPTN 084

Grouped Query Preferred Term	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Musculoskeletal pain (GQ)	54 (3.3)	286 (18.8)	49 (3.0)	244 (16.1)	2.7 (0.0, 5.4)
Back pain	12 (0.7)	127 (8.4)	23 (1.4)	115 (7.6)	0.8 (-1.2, 2.7)
Myalgia	12 (0.7)	43 (2.8)	6 (0.4)	31 (2.0)	0.8 (-0.3, 1.9)
Musculoskeletal pain	5 (0.3)	44 (2.9)	3 (0.2)	36 (2.4)	0.5 (-0.6, 1.7)
Muscle spasms	0	13 (0.9)	4 (0.2)	8 (0.5)	0.3 (-0.3, 0.9)
Muscle strain	2 (0.1)	16 (1.1)	0	13 (0.9)	0.2 (-0.5, 0.9)
Pain in extremity	5 (0.3)	26 (1.7)	2 (0.1)	23 (1.5)	0.2 (-0.7, 1.1)
Arthritis	0	3 (0.2)	1 (0.06)	2 (0.1)	0.1 (-0.2, 0.4)
Bursitis	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Flank pain	0	2 (0.1)	0	0	0.1 (-0.1, 0.3)
Groin pain	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Joint effusion	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Joint stiffness	0	2 (0.1)	0	1 (0.07)	0.1 (-0.2, 0.3)
Musculoskeletal disorder	0	2 (0.1)	0	0	0.1 (-0.1, 0.3)
Neck pain	2 (0.1)	8 (0.5)	1 (0.06)	6 (0.4)	0.1 (-0.4, 0.6)
Osteoarthritis	0	3 (0.2)	0	1 (0.07)	0.1 (-0.1, 0.4)
Tendonitis	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Torticollis	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Muscle tightness	0	5 (0.3)	0	5 (0.3)	-0.0 (-0.4, 0.4)
Musculoskeletal chest pain	7 (0.4)	27 (1.8)	4 (0.2)	27 (1.8)	-0.0 (-0.9, 0.9)
Costochondritis	0	4 (0.3)	2 (0.1)	5 (0.3)	-0.1 (-0.5, 0.3)
Joint swelling	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Musculoskeletal discomfort	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Pain in jaw	0	0	0	2 (0.1)	-0.1 (-0.3, 0.1)
Sacroiliitis	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Spinal osteoarthritis	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Arthralgia	12 (0.7)	38 (2.5)	4 (0.2)	44 (2.9)	-0.4 (-1.6, 0.8)
Rash (GQ)	47 (2.9)	165 (10.9)	61 (3.8)	131 (8.6)	2.2 (0.1, 4.3)
Dermatitis	4 (0.2)	26 (1.7)	3 (0.2)	13 (0.9)	0.9 (0.1, 1.7)
Rash pruritic	5 (0.3)	12 (0.8)	4 (0.2)	4 (0.3)	0.5 (0.0, 1.0)
Dermatitis allergic	6 (0.4)	40 (2.6)	8 (0.5)	34 (2.2)	0.4 (-0.7, 1.5)
Dermatitis contact	2 (0.1)	12 (0.8)	1 (0.06)	7 (0.5)	0.3 (-0.2, 0.9)
Prurigo	1 (0.06)	14 (0.9)	1 (0.06)	10 (0.7)	0.3 (-0.4, 0.9)
Pruritus	9 (0.6)	32 (2.1)	23 (1.4)	27 (1.8)	0.3 (-0.7, 1.3)
Rash	9 (0.6)	26 (1.7)	12 (0.7)	22 (1.5)	0.3 (-0.6, 1.1)
Pruritus allergic	0	5 (0.3)	1 (0.06)	2 (0.1)	0.2 (-0.1, 0.5)
Dermatitis atopic	0	4 (0.3)	0	3 (0.2)	0.1 (-0.3, 0.4)
Erythema	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Photosensitivity reaction	0	2 (0.1)	0	0	0.1 (-0.1, 0.3)
Rash erythematous	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Skin discoloration	1 (0.06)	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Skin exfoliation	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Skin hypopigmentation	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Drug eruption	1 (0.06)	0	0	0	0 (0, 0)
Macule	0	0	1 (0.06)	0	0 (0, 0)
Miliaria	0	2 (0.1)	1 (0.06)	2 (0.1)	-0.0 (-0.3, 0.3)
Perioral dermatitis	0	0	1 (0.06)	0	0 (0, 0)
Rash vesicular	0	0	1 (0.06)	0	0 (0, 0)
Dermatitis acneiform	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Lichen planus	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Rash follicular	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)

Grouped Query Preferred Term	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Rash macular	2 (0.1)	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Rash papular	3 (0.2)	10 (0.7)	2 (0.1)	11 (0.7)	-0.1 (-0.7, 0.5)
Rash pustular	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Skin reaction	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Rash maculo-papular	5 (0.3)	3 (0.2)	5 (0.3)	6 (0.4)	-0.2 (-0.6, 0.2)
Systemic injection site reactions (GQ)	11 (0.7)	79 (5.2)	10 (0.6)	60 (4.0)	1.2 (-0.2, 2.7)
Musculoskeletal pain	5 (0.3)	44 (2.9)	3 (0.2)	36 (2.4)	0.5 (-0.6, 1.7)
Hypotension	3 (0.2)	13 (0.9)	2 (0.1)	8 (0.5)	0.3 (-0.3, 0.9)
Pyrexia	3 (0.2)	19 (1.3)	5 (0.3)	16 (1.1)	0.2 (-0.6, 1.0)
Sciatica	0	4 (0.3)	0	3 (0.2)	0.1 (-0.3, 0.4)
STI (GQ)	22 (1.4)	506 (33.3)	29 (1.8)	490 (32.3)	1.0 (-2.4, 4.3)
Vulvovaginitis trichomonal	1 (0.06)	126 (8.3)	4 (0.2)	106 (7.0)	1.3 (-0.6, 3.2)
Trichomoniasis	0	19 (1.3)	0	12 (0.8)	0.5 (-0.3, 1.2)
Urogenital trichomoniasis	2 (0.1)	12 (0.8)	2 (0.1)	5 (0.3)	0.5 (-0.1, 1.0)
Gonorrhea	2 (0.1)	20 (1.3)	2 (0.1)	15 (1.0)	0.3 (-0.4, 1.1)
Syphilis	0	29 (1.9)	0	26 (1.7)	0.2 (-0.8, 1.1)
Anogenital warts	1 (0.06)	7 (0.5)	2 (0.1)	6 (0.4)	0.1 (-0.4, 0.5)
Chancroid	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Genital herpes simplex	0	2 (0.1)	0	0	0.1 (-0.1, 0.3)
Pelvic inflammatory disease	6 (0.4)	47 (3.1)	6 (0.4)	46 (3.0)	0.1 (-1.2, 1.3)
Secondary syphilis	1 (0.06)	0	0	0	0 (0, 0)
Syphilis genital	0	3 (0.2)	0	3 (0.2)	-0.0 (-0.3, 0.3)
Vaginitis chlamydial	1 (0.06)	0	0	0	0 (0, 0)
Bacterial vaginosis	2 (0.1)	36 (2.4)	1 (0.06)	37 (2.4)	-0.1 (-1.2, 1.0)
Genitourinary tract gonococcal infection	0	68 (4.5)	0	69 (4.6)	-0.1 (-1.6, 1.4)
Gonococcal infection	0	38 (2.5)	2 (0.1)	40 (2.6)	-0.1 (-1.3, 1.0)
Molluscum contagiosum	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Genitourinary chlamydia infection	3 (0.2)	144 (9.5)	2 (0.1)	146 (9.6)	-0.2 (-2.2, 1.9)
Genital herpes	1 (0.06)	3 (0.2)	1 (0.06)	7 (0.5)	-0.3 (-0.7, 0.1)
Sexually transmitted disease	2 (0.1)	34 (2.2)	4 (0.2)	39 (2.6)	-0.3 (-1.4, 0.8)
Chlamydial infection	1 (0.06)	109 (7.2)	5 (0.3)	140 (9.2)	-2.1 (-4.0, -0.1)
Anxiety disorder (GQ)	1 (0.06)	15 (1.0)	0	11 (0.7)	0.3 (-0.4, 0.9)
Post-traumatic stress disorder	0	3 (0.2)	0	0	0.2 (-0.0, 0.4)
Anxiety	0	9 (0.6)	0	8 (0.5)	0.1 (-0.5, 0.6)
Panic attack	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Panic disorder	0	2 (0.1)	0	1 (0.07)	0.1 (-0.2, 0.3)
Stress	1 (0.06)	2 (0.1)	0	1 (0.07)	0.1 (-0.2, 0.3)
Generalized anxiety disorder	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)

Grouped Query Preferred Term	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Sleep disorder (GQ)	51 (3.2)	30 (2.0)	42 (2.6)	28 (1.8)	0.1 (-0.8, 1.1)
Insomnia	15 (0.9)	22 (1.4)	15 (0.9)	20 (1.3)	0.1 (-0.7, 1.0)
Somnolence	31 (1.9)	7 (0.5)	27 (1.7)	5 (0.3)	0.1 (-0.3, 0.6)
Initial insomnia	1 (0.06)	0	1 (0.06)	0	0 (0, 0)
Poor quality sleep	0	1 (0.07)	0	1 (0.07)	-0.0 (-0.2, 0.2)
Sleep disorder	2 (0.1)	0	0	0	0 (0, 0)
Nightmare	3 (0.2)	0	1 (0.06)	1 (0.07)	-0.1 (-0.2, 0.1)
Terminal insomnia	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Pyrexia (GQ)	17 (1.1)	55 (3.6)	20 (1.2)	55 (3.6)	-0.0 (-1.3, 1.3)
Pyrexia	3 (0.2)	19 (1.3)	5 (0.3)	16 (1.1)	0.2 (-0.6, 1.0)
Feeling hot	0	1 (0.07)	1 (0.06)	1 (0.07)	-0.0 (-0.2, 0.2)
Chills	3 (0.2)	4 (0.3)	0	5 (0.3)	-0.1 (-0.5, 0.3)
Influenza like illness	11 (0.7)	31 (2.0)	14 (0.9)	34 (2.2)	-0.2 (-1.2, 0.8)
Fatigue (GQ)	33 (2.0)	32 (2.1)	40 (2.5)	35 (2.3)	-0.2 (-1.2, 0.8)
Asthenia	6 (0.4)	2 (0.1)	6 (0.4)	3 (0.2)	-0.1 (-0.4, 0.2)
Fatigue	25 (1.5)	16 (1.1)	29 (1.8)	17 (1.1)	-0.1 (-0.8, 0.7)
Malaise	2 (0.1)	14 (0.9)	6 (0.4)	15 (1.0)	-0.1 (-0.8, 0.6)
HSR (GQ)	14 (0.9)	64 (4.2)	23 (1.4)	66 (4.4)	-0.1 (-1.6, 1.3)
Pruritus allergic	0	5 (0.3)	1 (0.06)	2 (0.1)	0.2 (-0.1, 0.5)
Arthritis	0	3 (0.2)	1 (0.06)	2 (0.1)	0.1 (-0.2, 0.4)
Oedema peripheral	1 (0.06)	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Peripheral swelling	0	4 (0.3)	0	3 (0.2)	0.1 (-0.3, 0.4)
Drug eruption	1 (0.06)	0	0	0	0 (0, 0)
Drug hypersensitivity	0	0	1 (0.06)	0	0 (0, 0)
Eosinophilia	1 (0.06)	1 (0.07)	0	1 (0.07)	-0.0 (-0.2, 0.2)
Gingival swelling	1 (0.06)	0	0	0	0 (0, 0)
Hypersensitivity	1 (0.06)	7 (0.5)	5 (0.3)	5 (0.3)	0.1 (-0.3, 0.6)
Lip swelling	0	1 (0.07)	0	1 (0.07)	-0.0 (-0.2, 0.2)
Periorbital swelling	0	1 (0.07)	0	1 (0.07)	-0.0 (-0.2, 0.2)
Swelling of eyelid	1 (0.06)	0	0	0	0 (0, 0)
Urticaria	3 (0.2)	15 (1.0)	4 (0.2)	15 (1.0)	-0.0 (-0.7, 0.7)
Joint swelling	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Mouth ulceration	1 (0.06)	2 (0.1)	1 (0.06)	4 (0.3)	-0.1 (-0.4, 0.2)
Stomatitis	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Swelling	0	0	1 (0.06)	2 (0.1)	-0.1 (-0.3, 0.1)
Swelling face	0	1 (0.07)	0	2 (0.1)	-0.1 (-0.3, 0.2)
Conjunctivitis	4 (0.2)	26 (1.7)	9 (0.6)	30 (2.0)	-0.3 (-1.2, 0.7)

Grouped Query Preferred Term	CAB Step 1 N=1,614 n (%)	CAB Step 2 N=1,519 n (%)	TDF/FTC Step 1 N=1,610 n (%)	TDF/FTC Step 2 N=1,516 n (%)	Risk Difference (95% CI)
Mood disorder (GQ)	0	9 (0.6)	2 (0.1)	13 (0.9)	-0.3 (-0.9, 0.3)
Mood swings	0	1 (0.07)	0	0	0.1 (-0.1, 0.2)
Suicidal ideation	0	2 (0.1)	0	0	0.1 (-0.1, 0.3)
Depression	0	7 (0.5)	0	7 (0.5)	-0.0 (-0.5, 0.5)
Intentional self-injury	0	1 (0.07)	1 (0.06)	1 (0.07)	-0.0 (-0.2, 0.2)
Depressed mood	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Depression suicidal	0	0	0	1 (0.07)	-0.1 (-0.2, 0.1)
Depressive symptom	0	0	0	2 (0.1)	-0.1 (-0.3, 0.1)
Major depression	0	0	1 (0.06)	1 (0.07)	-0.1 (-0.2, 0.1)
Suicide attempt	0	0	0	2 (0.1)	-0.1 (-0.3, 0.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE with an onset date on or after the start of treatment and before 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively).
Duration is median 29 days for Step 1 groups and median 452 days for Step 2 groups.
Risk difference column shows difference (with 95% confidence interval) between step 2 groups.
Abbreviations: CAB, cabotegravir; CI, confidence interval; GQ, grouped query; HSR, hypersensitivity reaction; N, number of subjects in treatment arm; n, number of subjects with adverse event; STI, sexually transmitted infection; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

The type, severity, and frequency of ISRs are summarized in Section 7.6.3.1. See Tables 119 and 120 for the specific ISR preferred terms reported in each trial.

Table 119. Injection Site Reactions by Preferred Term, Injection Safety Population, Trial HPTN 083

Preferred Term	CAB N=2,117 n (%)	CAB Events	TDF/FTC N=2,081 n (%)	TDF/FTC Events	Risk Difference (95% CI)
Any AE	1,740 (82.2)	9,470	724 (34.8)	1,629	47.4 (44.78, 50.02)
Injection site pain	1,713 (80.9)	7,884	686 (33)	1,486	47.95 (45.33, 50.57)
Injection site nodule	263 (12.4)	507	13 (0.6)	14	11.8 (10.35, 13.24)
Injection site induration	255 (12)	378	7 (0.3)	8	11.71 (10.3, 13.12)
Injection site swelling	206 (9.7)	325	9 (0.4)	9	9.3 (8, 10.59)
Injection site bruising	63 (3)	91	26 (1.2)	26	1.73 (0.86, 2.59)
Injection site erythema	63 (3)	71	11 (0.5)	11	2.45 (1.66, 3.24)
Injection site warmth	60 (2.8)	75	9 (0.4)	9	2.4 (1.64, 3.16)
Injection site pruritus	46 (2.2)	59	24 (1.2)	28	1.02 (0.25, 1.79)
Injection site anesthesia	25 (1.2)	31	18 (0.9)	20	0.32 (-0.29, 0.92)
Injection site hematoma	13 (0.6)	13	5 (0.2)	5	0.37 (-0.02, 0.77)
Injection site discoloration	10 (0.5)	10	0	0	0.47 (0.18, 0.76)
Injection site reaction	10 (0.5)	16	2 (0.1)	6	0.38 (0.06, 0.7)
Injection site abscess	2 (0.1)	2	0	0	0.09 (-0.04, 0.23)
Immediate postinjection reaction	1 (0)	1	1 (0)	1	0 (-0.13, 0.13)
Injection site discomfort	1 (0)	1	2 (0.1)	4	-0.05 (-0.21, 0.11)
Injection site hemorrhage	1 (0)	1	1 (0)	1	0 (-0.13, 0.13)
Injection site infection	1 (0)	1	0	0	0.05 (-0.05, 0.14)
Injection site irritation	1 (0)	1	0	0	0.05 (-0.05, 0.14)
Injection site oedema	1 (0)	1	0	0	0.05 (-0.05, 0.14)
Injection site rash	1 (0)	1	0	0	0.05 (-0.05, 0.14)
Injection site scar	1 (0)	1	0	0	0.05 (-0.05, 0.14)

Preferred Term	CAB N=2,117 n (%)	CAB Events	TDF/FTC N=2,081 n (%)	TDF/FTC Events	Risk Difference (95% CI)
Injection site hypertrophy	0	0	1 (0)	1	-0.05 (-0.14, 0.05)

Source: adaeisr.xpt; Software: R
Treatment-emergent adverse events defined as any AE after the first dose of study drug and until 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively).
Median duration is 457 days.
Risk difference column shows difference (with 95% confidence interval) between treatment and comparator.
Abbreviations: AE, adverse event; CAB, cabotegravir; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 120. Injection Site Reactions by Preferred Term, Injection Safety Population, Trial HPTN 084

Preferred Term	CAB N=1,519 n (%)	CAB Events	TDF/FTC N=1,516 n (%)	TDF/FTC Events	Risk Difference (95% CI)
Any AE	578 (38.1)	1,212	166 (10.9)	239	27.1 (24.2, 30.01)
Injection site pain	520 (34.2)	825	145 (9.6)	191	24.67 (21.86, 27.48)
Injection site swelling	104 (6.8)	119	5 (0.3)	6	6.52 (5.21, 7.82)
Injection site nodule	80 (5.3)	92	4 (0.3)	4	5 (3.85, 6.16)
Injection site induration	70 (4.6)	73	4 (0.3)	4	4.34 (3.26, 5.43)
Injection site pruritus	33 (2.2)	37	19 (1.3)	20	0.92 (0, 1.84)
Injection site erythema	29 (1.9)	30	3 (0.2)	4	1.71 (0.99, 2.43)
Injection site abscess	10 (0.7)	12	5 (0.3)	5	0.33 (-0.17, 0.83)
Injection site discoloration	8 (0.5)	8	0	0	0.53 (0.16, 0.89)
Injection site bruising	7 (0.5)	7	0	0	0.46 (0.12, 0.8)
Injection site anesthesia	6 (0.4)	6	3 (0.2)	3	0.2 (-0.19, 0.58)
Injection site warmth	2 (0.1)	2	0	0	0.13 (-0.05, 0.31)
Injection site infection	1 (0.1)	1	0	0	0.07 (-0.06, 0.19)
Injection site reaction	0	0	2 (0.1)	2	-0.13 (-0.31, 0.05)

Source: adaeisr.xpt; Software: R
Treatment-emergent adverse events defined as any AE after the first dose of study drug and until 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively).
Median duration is 452 days.
Risk difference column shows difference (with 95% confidence interval) between treatment and comparator.
Abbreviations: AE, adverse event; CAB, cabotegravir; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

The STI analyses presented in Section 7.6.3.9 show the rates of STIs in the safety population and during the on-blinded study product portions of the trial. The Applicant's STI analyses, conducted from an efficacy perspective rather than a safety perspective, are shown below. The conclusions are the same regardless of the approach taken for the analyses.

Table 121. Summary of Incident Sexually Transmitted Infections, mITT Population, Trial HPTN 083 (Applicant's Analysis)

	CAB (N=2280)	TDF/FTC (N=2281)
Syphilis		
Participants infected among participants tested, n/N (%)	352/1933 (18)	350/1902 (18)
Positive tests among all tests performed[a], n/N (%)	461/6028 (8)	459/5952 (8)
Incidence rate, per 100 PY	16.58	16.64
Gonorrhoea (urine)		
Participants infected among participants tested, n/N (%)	71/1901 (4)	51/1868 (3)
Positive tests among all tests performed[a], n/N (%)	76/5584 (1)	58/5455 (1)
Incidence rate, per 100 PY	2.76	2.13
Gonorrhoea (rectal)		
Participants infected among participants tested, n/N (%)	251/1895 (13)	253/1865 (14)
Positive tests among all tests performed[a], n/N (%)	302/5512 (5)	297/5406 (5)
Incidence rate, per 100 PY	11.06	10.95
Chlamydia (urine)		
Participants infected among participants tested, n/N (%)	110/1901 (6)	117/1868 (6)
Positive tests among all tests performed[a], n/N (%)	122/5582 (2)	127/5456 (2)
Incidence rate, per 100 PY	4.44	4.67
Chlamydia (rectal)		
Participants infected among participants tested, n/N (%)	336/1895 (18)	383/1865 (21)
Positive tests among all tests performed[a], n/N (%)	430/5521 (8)	482/5419 (9)
Incidence rate, per 100 PY	15.75	17.76
Hepatitis C		
Participants infected among participants tested, n/N (%)	8/1403 (<1)	11/1400 (<1)
Positive tests among all tests performed[a], n/N (%)	10/1999 (<1)	12/2004 (<1)
Incidence rate, per 100 PY	0.39	0.53

Data Source: Table 2.011

Notes:

The same participant can be infected more than once.

The percentages are based on the number of participants in the mITT population.

a. STI tests were performed every 6 months after the enrollment. This summary also includes STI tests that were not planned but were performed by sites due to suspected infections.

Table 122. Summary of Incident Sexually Transmitted Infections, mITT Population, Trial HPTN 084 (Applicant's Analysis)

	CAB (N=1614) n/N (%)	TDF/FTC (N=1610) n/N (%)
Active Syphilis		
Participants infected among participants tested	19/1365 (1)	19/1355 (1)
Positive tests among all tests performed[a,b]	22/3161 (<1)	29/3124 (<1)
Incidence rate,per 100 PY	1.30	1.73
Gonorrhoea		
Participants infected among participants tested	116/1371 (8)	123/1360 (9)
Positive tests among all tests performed[a,b]	122/3230 (4)	137/3205 (4)
Incidence rate, per 100 PY	7.20	8.15
Chlamydia		
Participants infected among participants tested	271/1371 (20)	285/1360 (21)
Positive tests among all tests performed[a,b]	311/3230 (10)	348/3205 (11)
Incidence rate, per 100 PY	18.34	20.70
Trichomonas vaginalis		
Participants infected among participants tested	146/1361 (11)	121/1350 (9)
Positive tests among all tests performed[a,b]	180/3171 (6)	148/3158 (5)
Incidence rate, per 100 PY	10.68	8.89
Hepatitis C		
Participants infected among participants tested	5/1006 (<1)	4/1002 (<1)
Positive tests among all tests performed[a,c]	7/1140 (<1)	5/1136 (<1)
Incidence rate, per 100 PY	0.41	0.33

Data Source: Table 2.011
Note: The percentages are based on the number of participants in the mITT Population.
Note: The same participant could be infected more than once, except for Hepatitis C.
Note: A participant was considered as diagnosed with active Syphilis if the non-Treponemal test result was reactive, the Treponemal test result was reactive/positive, and the titer was 1:8 or greater.
Note: A participant was considered as tested positive for Gonorrhea if test results for either Gonorrhea (urine) or Gonorrhea (vaginal swab) results were positive.
Note: A participant was considered as tested positive for Chlamydia if test results for either Chlamydia (urine) or Chlamydia (vaginal swab) results were positive.
Note: A participant was considered as tested positive for *Trichomonas vaginalis* if test results for either Trichomonas (rapid test) or *Trichomonas vaginalis* (wet mount) results were positive.
a. This summary also includes tests that were not planned but were performed due to suspected infections.
b. After enrollment, STI tests were routinely performed at Week 33 and every 24 weeks thereafter.
c. Hepatitis C was routinely tested at Week 57 and every 48 weeks thereafter.

17.5. Laboratory Findings, HPTN 083 and HPTN 084

Key laboratory parameters are presented and discussed in Sections 7.6.1.6 and 7.6.2.6. Additional laboratory parameters for HPTN 083 and HPTN 084 are presented in 123 and 124.

Table 123. Additional Laboratory Parameter Values Worsened From Baseline, Safety Population, Trial HPTN 083

Laboratory Parameter	CAB N=2,281 n (%)	TDF/FTC N=2,285 n (%)	Risk Difference (%) (95% CI)
Phosphate (mmol/L) decreased			
Any grade	517 (22.7)	592 (25.9)	-3.2 (-5.7, -0.8)
Grade 3-4	5 (0.2)	3 (0.1)	0.1 (-0.2, 0.3)
Amylase (IU/L) increased			
Any grade	398 (17.4)	402 (17.6)	-0.1 (-2.3, 2.1)
Grade 3-4	16 (0.7)	14 (0.6)	0.1 (-0.4, 0.6)
Calcium (mmol/L) increased			
Any grade	101 (4.4)	75 (3.3)	1.1 (0, 2.3)
Grade 3-4	1 (0)	0	0 (0, 0.1)
Calcium (mmol/L) decreased			
Any grade	76 (3.3)	93 (4.1)	-0.7 (-1.8, 0.4)
Grade 3-4	0	0	0 (0, 0)
Fasting glucose (mg/dL) increased			
Any grade	51 (2.2)	41 (1.8)	0.4 (-0.4, 1.3)
Grade 3-4	5 (0.2)	3 (0.1)	0.1 (-0.2, 0.3)
Fasting glucose (mg/dL) decreased			
Any grade	15 (0.7)	12 (0.5)	0.1 (-0.3, 0.6)
Grade 3-4	0	2 (0.1)	-0.1 (-0.2, 0)
Neutrophils (10^9/L) decreased			
Any grade	89 (3.9)	126 (5.5)	-1.6 (-2.8, -0.4)
Grade 3-4	6 (0.3)	12 (0.5)	-0.3 (-0.6, 0.1)
Lymphocytes (10^9/L) decreased			
Any grade	36 (1.6)	30 (1.3)	0.3 (-0.4, 1)
Grade 3-4	9 (0.4)	9 (0.4)	0 (-0.4, 0.4)
Leukocytes (10^9/L) decreased			
Any grade	26 (1.1)	36 (1.6)	-0.4 (-1.1, 0.2)
Grade 3-4	0	0	0 (0, 0)
Hemoglobin (g/L) decreased			
Any grade	23 (1)	25 (1.1)	-0.1 (-0.7, 0.5)
Grade 3-4	3 (0.1)	0	0.1 (0, 0.3)
Platelets (10^9/L) decreased			
Any grade	22 (1)	22 (1)	0 (-0.6, 0.6)
Grade 3-4	1 (0)	0	0 (0, 0.1)

Source: ad b.xpt from submission 0010, received July 20, 2021; Software: R
Median duration is 457 days.
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CAB, cabotegravir; CI, confidence interval; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Table 124. Additional Laboratory Parameter Values Worsened From Baseline, Safety Population, Trial HPTN 084

Laboratory Parameter	CAB N=1,614 n (%)	TDF/FTC N=1,610 n (%)	Risk Difference (%) (95% CI)
Amylase (IU/L) increased			
Any grade	464 (28.7)	440 (27.3)	1.4 (-1.7, 4.5)
Grade 3-4	4 (0.2)	5 (0.3)	-0.1 (-0.4, 0.3)
Calcium (mmol/L) decreased			
Any grade	109 (6.8)	136 (8.4)	-1.7 (-3.5, 0.1)
Grade 3-4	1 (0.1)	3 (0.2)	-0.1 (-0.4, 0.1)
Calcium (mmol/L) increased			
Any grade	86 (5.3)	67 (4.2)	1.2 (-0.3, 2.6)
Grade 3-4	1 (0.1)	0	0.1 (-0.1, 0.2)
Fasting glucose (mg/dL) increased			
Any grade	19 (1.2)	19 (1.2)	0 (-0.7, 0.7)
Grade 3-4	0	1 (0.1)	-0.1 (-0.2, 0.1)
Fasting glucose (mg/dL) decreased			
Any grade	9 (0.6)	12 (0.7)	-0.2 (-0.7, 0.4)
Grade 3-4	0	0	0 (0, 0)
Creatinine clearance (mL/min) decreased			
Any grade	1,103 (68.3)	1,123 (69.8)	-1.4 (-4.6, 1.8)
Grade 3-4	110 (6.8)	121 (7.5)	-0.7 (-2.5, 1.1)
Neutrophils (10^9/L) decreased			
Any grade	104 (6.4)	90 (5.6)	0.9 (-0.8, 2.5)
Grade 3-4	7 (0.4)	4 (0.2)	0.2 (-0.2, 0.6)
Hemoglobin (g/L) decreased			
Any grade	87 (5.4)	95 (5.9)	-0.5 (-2.1, 1.1)
Grade 3-4	7 (0.4)	6 (0.4)	0.1 (-0.4, 0.5)
Platelets (10^9/L) decreased			
Any grade	43 (2.7)	27 (1.7)	1 (0, 2)
Grade 3-4	2 (0.1)	0	0.1 (0, 0.3)
Leukocytes (10^9/L) decreased			
Any grade	25 (1.5)	30 (1.9)	-0.3 (-1.2, 0.6)
Grade 3-4	0	1 (0.1)	-0.1 (-0.2, 0.1)
Lymphocytes (10^9/L) decreased			
Any grade	9 (0.6)	8 (0.5)	0.1 (-0.4, 0.6)
Grade 3-4	3 (0.2)	3 (0.2)	0 (-0.3, 0.3)

Source: ad b.xpt from submission 0012, received July 23, 2021; Software: R
Median duration is 452 days.
Based on DAIDS Adverse Event Grading Tables Version 2.1
Abbreviations: CAB, cabotegravir; CI, confidence interval; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

17.6. Safety Analyses by Special Subgroups: HPTN 083 and HPTN 084

The rate of AEs was compared across key subgroups of participants (by gender, age, race, and ethnicity). These analyses were conducted separately for HPTN 083 and HPTN 084. Within each of these trials, events occurring in Steps 1 and 2 were combined.

In trial HPTN 083, the rate of AEs was comparable across genders, age, and ethnicities, noting that some of these subgroups were quite small. A higher proportion of Asian participants receiving CAB experienced AEs (99.0%) compared to American Indian or Alaska Native

(92.7%), Black or African American (93.3%) and White (97.11%) participants. However, this variability by race is of unclear significance.

Table 125. Adverse Events by Demographic Subgroup, Safety Population, Trial HPTN 083

Characteristic	CAB N=2,281 n/N_s (%)	TDF/FTC N=2,285 n/N_s (%)	Risk Difference (95% CI)
Gender, n(%)			
Man	1,917/2,012 (95.3)	1,877/1,980 (94.8)	0.5 (-0.9, 1.8)
No answer	3/3 (100)	1/1 (100)	0 (0, 0)
Transgender woman	254/266 (95.5)	279/304 (91.8)	3.7 (-0.3, 7.7)
Age group, years, n (%)			
<50	2,111/2,215 (95.3)	2,102/2,229 (94.3)	1.0 (-0.3, 2.3)
≥50	63/66 (95.5)	55/56 (98.2)	-2.8 (-8.9, 3.3)
Race, n (%)			
American Indian or Alaska Native	571/616 (92.7)	535/599 (89.3)	3.4 (0.2, 6.6)
Asian	413/417 (99.0)	397/406 (97.8)	1.3 (-0.5, 3.0)
Black or African American	526/564 (93.3)	538/568 (94.7)	-1.5 (-4.2, 1.3)
Mixed Race	46/48 (95.8)	53/54 (98.1)	-2.3 (-9.0, 4.4)
Native Hawaiian or Other Pacific Islander	5/5 (100)	2/2 (100)	0 (0, 0)
Unknown	13/13 (100)	7/7 (100)	0 (0, 0)
White	600/618 (97.1)	625/649 (96.3)	0.8 (-1.2, 2.8)
Ethnicity, n (%)			
Hispanic or Latino	985/1,043 (94.4)	986/1,066 (92.5)	1.9 (-0.2, 4.0)
Not Hispanic or Latino	1,189/1,238 (96.0)	1,170/1,218 (96.1)	-0.0 (-1.6, 1.5)
Not Reported	0/0 (NA)	1/1 (100)	NA (NA)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE after the first dose of study drug and until 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively). For those with no injections, events after the first of 1 day after the date of discontinuation or 120 days after randomization were considered not treatment-emergent.
Median duration is 457 days.
Risk difference column shows difference (with 95% confidence interval) between groups.
Abbreviations: CAB, cabotegravir; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm; NA, not applicable; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

As in trial HPTN 083, there were no apparent differences in safety across gender, age, or race subgroups in HPTN 084. Notably, these subgroup analyses were very limited as all but two CAB participants were Black or African American, all were less than 50 years of age, and all were not Hispanic or Latino.

Table 126. Adverse Events by Demographic Subgroup, Safety Population, Trial HPTN 084

Characteristic	CAB N=1,614 n/N_s (%)	TDF/FTC N=1,610 n/N_s (%)	Risk Difference (95% CI)
Gender			
Woman, cisgender	1,554/1,612 (96.4)	1,537/1,607 (95.6)	0.8 (-0.6, 2.1)
Man, cisgender	0/0 (NA)	3/3 (100)	NA (NA)
Transgender man (female to male)	2/2 (100)	0/0 (NA)	NA (NA)
Age group 1, years			
18-25	892/929 (96.0)	876/921 (95.1)	0.9 (-1.0, 2.8)
26-35	530/547 (96.9)	530/554 (95.7)	1.2 (-1.0, 3.5)
36-45	134/138 (97.1)	134/135 (99.3)	-2.2 (-5.3, 1.0)

Characteristic	CAB N=1,614 n/Ns (%)	TDF/FTC N=1,610 n/Ns (%)	Risk Difference (95% CI)
Race			
Asian	2/2 (100)	3/3 (100)	0 (0, 0)
Black or African American	1,554/1,612 (96.4)	1,536/1,606 (95.6)	0.8 (-0.6, 2.1)
White	0/0 (NA)	1/1 (100)	NA (NA)
Ethnicity			
Not Hispanic or Latino	1,556/1,614 (96.4)	1,540/1,610 (95.7)	0.8 (-0.6, 2.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE after the first dose of study drug and until 6 or 10 weeks after the last injection (if number of injections is 1 or ≥2, respectively).
Median duration is 452 days.
Risk difference column shows difference (with 95% confidence interval) between groups.
Abbreviations: CAB, cabotegravir; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; Ns, total number of patients for each specific subgroup and were assigned to that specific arm; NA, not applicable; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

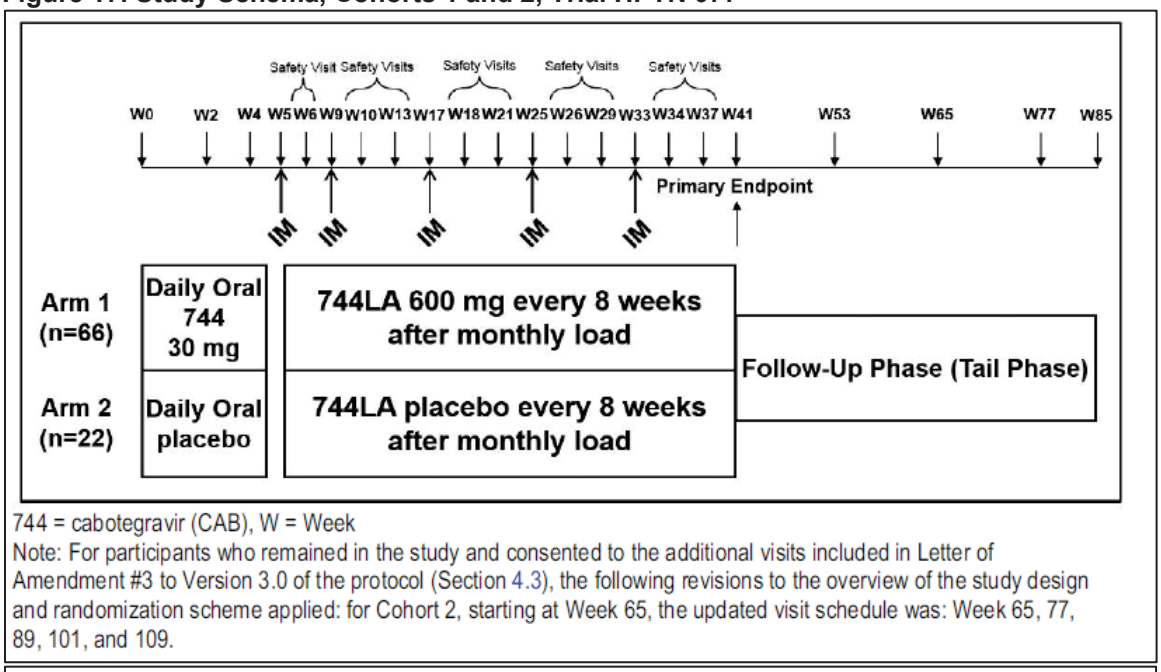
17.7. Phase 2 Safety Data

As noted in Section 7.4, the phase 2 clinical trials of CAB LA in HIV-1 uninfected adults (HPTN 077 and ÉCLAIR) studied different dosing regimens than HPTN 083 and HPTN 084. Therefore, the phase 2 safety data were not pooled with the phase 3 safety data. Key safety analyses from each of these phase 2 trials will be presented below.

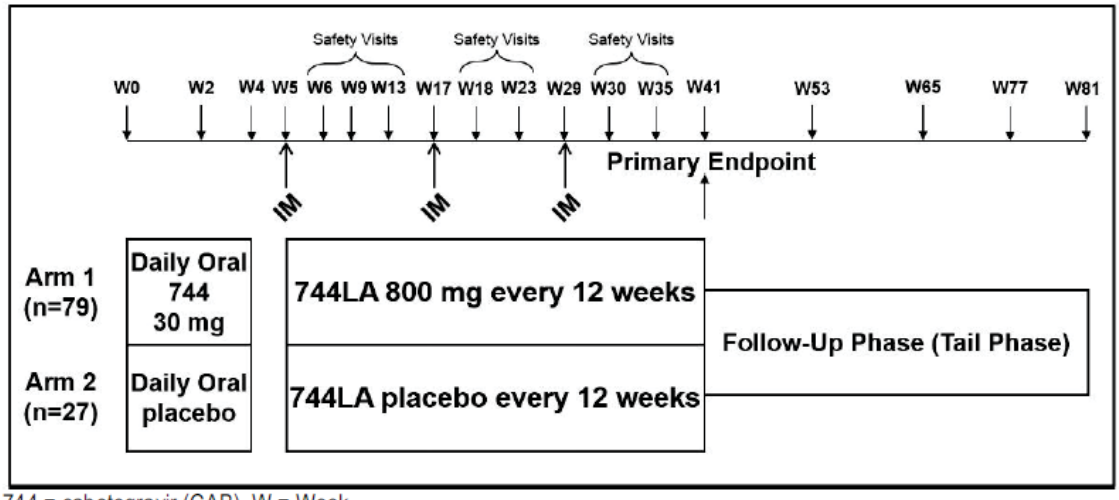
17.7.1. HPTN 077

HPTN 077 was a phase 2a trial to assess the safety, tolerability, and acceptability of CAB LA for PrEP in HIV-1 uninfected men and women enrolled across 2 cohorts. The study schema for Cohorts 1 and 2 are shown Figure 17. Of note, for the HPTN safety analyses, “On-Treatment” was defined as the time between the beginning of the OLI phase and the end of the follow-up phase.

Figure 17. Study Schema, Cohorts 1 and 2, Trial HPTN 077



744 = cabotegravir (CAB), W = Week
Note: For participants who remained in the study and consented to the additional visits included in Letter of Amendment #3 to Version 3.0 of the protocol (Section 4.3), the following revisions to the overview of the study design and randomization scheme applied: for Cohort 2, starting at Week 65, the updated visit schedule was: Week 65, 77, 89, 101, and 109.



744 = cabotegravir (CAB), W = Week
Note: For participants who remained in the study and consented to the additional visits included in Letter of Amendment #3 to Version 3.0 of the protocol (Section 4.3), the following revisions to the overview of the study design and randomization scheme applied: for Cohort 1, starting at Week 65, the updated visit schedule was: Week 65, 77, 89, 101, and 105.

Source: HPTN 077 CSR

As shown in Table 127, in addition to ISRs, other ADRs reported more frequently in CAB participants included pyrexia, headache, dizziness, paraesthesia, and nausea. Musculoskeletal and skin ADRs were also more common among CAB participants at the system organ class level.

Table 127. Summary of On-Treatment Drug-Related Adverse Events in at Least 2 Participants in Either Treatment Group, Trial HPTN 077

System Organ Class Preferred Term	CAB (N=151) n (%)	Placebo (N=48) n (%)
Any Drug-related Adverse Event	138 (91.4)	39 (81.3)
General disorders and administration site conditions	118 (78.1)	15 (31.3)
Injection site pain	113 (74.8)	9 (18.8)
Injection site induration	23 (15.2)	1 (2.1)
Injection site bruising	20 (13.2)	2 (4.2)
Injection site swelling	11 (7.3)	0
Injection site erythema	10 (6.6)	0
Fatigue	7 (4.6)	5 (10.4)
Pyrexia	7 (4.6)	0
Injection site nodule	7 (4.6)	0
Injection site reaction	4 (2.6)	0
Injection site pruritus	4 (2.6)	0
Injection site warmth	3 (2.0)	0
Pain	2 (1.3)	0
Injection site hemorrhage	2 (1.3)	0
Malaise	2 (1.3)	0
Investigations	83 (55.0)	31 (64.6)
Creatinine renal clearance decreased	33 (21.9)	12 (25.0)
Blood bicarbonate decreased	22 (14.6)	9 (18.8)
Amylase increased	16 (10.6)	4 (8.3)
Blood magnesium decreased	16 (10.6)	8 (16.7)
Alanine aminotransferase increased	14 (9.3)	4 (8.3)
Lipase increased	14 (9.3)	7 (14.6)
Blood phosphorus decreased	12 (7.9)	6 (12.5)
Blood creatinine increased	11 (7.3)	2 (4.2)
Blood creatine phosphokinase increased	10 (6.6)	5 (10.4)
Blood glucose decreased	7 (4.6)	2 (4.2)
Aspartate aminotransferase increased	6 (4.0)	1 (2.1)
Blood sodium increased	5 (3.3)	1 (2.1)
Low density lipoprotein increased	4 (2.6)	0
Blood calcium increased	4 (2.6)	2 (4.2)
Platelet count decreased	3 (2.0)	0
Blood glucose increased	2 (1.3)	0
Blood calcium decreased	2 (1.3)	2 (4.2)
Bilirubin conjugated increased	3 (2.0)	1 (2.1)
Blood pressure increased	2 (1.3)	0
Electrocardiogram QT prolonged	2 (1.3)	0
Blood bilirubin increased	2 (1.3)	2 (4.2)
Blood cholesterol increased	2 (1.3)	0
Blood magnesium increased	2 (1.3)	0
Nervous system disorders	45 (29.8)	10 (20.8)
Headache	34 (22.5)	7 (14.6)
Dizziness	14 (9.3)	2 (4.2)
Paraesthesia	7 (4.6)	0

Continued

Table 127, continued

System Organ Class Preferred Term	CAB (N=151) n (%)	Placebo (N=48) n (%)
Hypoaesthesia	5 (3.3)	1 (2.1)
Somnolence	3 (2.0)	0
Hypersomnia	2 (1.3)	0
Gastrointestinal disorders	33 (21.9)	8 (16.7)
Nausea	14 (9.3)	2 (4.2)
Dry mouth	4 (2.6)	0
Abdominal pain	3 (2.0)	0
Diarrhea	3 (2.0)	1 (2.1)
Abdominal distension	2 (1.3)	0
Vomiting	2 (1.3)	0
Musculoskeletal and connective tissue disorders	20 (13.2)	4 (8.3)
Myalgia	9 (6.0)	2 (4.2)
Pain in extremity	4 (2.6)	0
Back pain	3 (2.0)	0
Skin and subcutaneous tissue disorders	15 (9.9)	3 (6.3)
Pruritus	3 (2.0)	1 (2.1)
Pruritus generalized	3 (2.0)	0
Dermatitis allergic	2 (1.3)	0
Hyperhidrosis	2 (1.3)	0
Urticaria papular	2 (1.3)	0
Metabolism and nutrition disorders	19 (12.6)	7 (14.6)
Hypoglycemia	6 (4.0)	1 (2.1)
Hypophosphatemia	5 (3.3)	1 (2.1)
Increased appetite	3 (2.0)	2 (4.2)
Abnormal loss of weight	2 (1.3)	0
Hypernatremia	1 (0.7)	2 (4.2)
Psychiatric disorders	15 (9.9)	4 (8.3)
Insomnia	6 (4.0)	1 (2.1)
Abnormal dreams	6 (4.0)	2 (4.2)
Renal and urinary disorders	3 (2.0)	1 (2.1)
Proteinuria	2 (1.3)	0
Reproductive system and breast disorders	2 (1.3)	2 (4.2)
Dysfunctional uterine bleeding	2 (1.3)	1 (2.1)
Vascular disorders	2 (1.3)	0
Hypertension	2 (1.3)	0

Source: HPTN 077 CSR
Abbreviations: CAB, cabotegravir

The rate of treatment discontinuations due to AEs was higher in the CAB arm than in the placebo arm. The only AEs leading to treatment discontinuation in more than one CAB participant were headache and urticaria papular.

Table 128. Summary of AEs Leading to Withdrawal/Permanent Discontinuation of Study Drug, Trial HPTN 077

Preferred Term	CAB (N=151) n	Placebo (N=43) n
AEs leading to withdrawal during study	18	2
AEs Leading to withdrawal during the OLI Phase	6	0
Abnormal dreams	1	0
Alanine aminotransferase increased	1	0
Aspartate aminotransferase increased	1	0
Constipation	1	0
Dizziness	1	0
Headache	1	0
Insomnia	1	0
Lipase increased	1	0
Mood swings	1	0
Vomiting	1	0
AEs leading to withdrawal during Injection Phase	11	2
Headache	2	0
Urticaria papular	2	0
Acute kidney injury	1	0
Back pain	1	0
Dry mouth	1	0
Injection site pain	1	0
Myalgia	1	0
Pseudopapilloedema	1	0
Pain in extremity	1	0
Pruritus	1	0
Seizure	1	0
Sensory loss	1	0
Urethritis gonococcal	1	0
Vertigo positional	1	0
Alanine aminotransferase increased	0	1
Lipase increased	0	1
AEs leading to withdrawal during the Tail Phase	1	0
Headache	1	0

Source: HPTN 077 CSR
Abbreviations: AE, adverse event; CAB, cabotegravir; OLI, oral lead-in

Overall, 12 participants experienced 14 SAEs (11 participants in the CAB treatment group; 2 in the placebo group). Of note, nine of these SAEs occurred during the Tail Phase and will not be discussed. The remaining five SAEs all occurred during the injection phase and included vertigo (n=1), sensory loss in upper limb (n=1), acute kidney injury (n=1), and laryngitis (n=1) in CAB participants and cholelithiasis (n=1) in a placebo participant. Of these injection phase SAEs, vertigo and sensory loss in upper limb were considered to be related to study drug by the investigator and led to study withdrawal. There were no fatal SAEs reported.

Laboratory results were reviewed and revealed that ALT, AST, creatine kinase and creatinine abnormalities were more common among CAB participants than among placebo participants.

Table 129. Elevation of Liver Chemistry and Other Laboratory Test Events On-Treatment, Trial HPTN 077

Laboratory Parameter Grade	Overall		Cohort 1		Cohort 2	
	CAB (N=151) n (%)	Placebo (N=48) n (%)	CAB (N=82) n (%)	Placebo (N=28) n (%)	CAB (N=69) n (%)	Placebo (N=20) n (%)
ALT (IU/L)						
Grade 1	17 (11.3)	3 (6.3)	8 (9.8)	0	9 (13.0)	3 (15.0)
Grade 2	2 (1.3)	1 (2.1)	2 (2.4)	1 (3.6)	0	0
Grade 3	1 (0.7)	1 (2.1)	1 (1.2)	1 (3.6)	0	0
Aspartate Aminotransferase (IU/L)						
Grade 1	15 (9.9)	2 (4.2)	7 (8.5)	1 (3.6)	8 (11.6)	1 (5.0)
Grade 2	3 (2.0)	1 (2.1)	3 (3.7)	1 (3.6)	0	0
Grade 3	0	1 (2.1)	0	1 (3.6)	0	0
Bilirubin (μmol/L)						
Grade 1	6 (4.0)	3 (6.3)	2 (2.4)	1 (3.6)	4 (5.8)	2 (10.0)
Grade 2	1 (0.7)	0	1 (1.2)	0	0	0
Alkaline Phosphatase (IU/L)						
Grade 1	2 (1.3)	2 (4.2)	2 (2.4)	1 (3.6)	0	1 (5.0)
Creatine Kinase (IU/L)						
Grade 1	17 (11.3)	3 (6.3)	9 (11.0)	2 (7.1)	8 (11.6)	1 (5.0)
Grade 2	3 (2.0)	3 (6.3)	2 (2.4)	2 (7.1)	1 (1.4)	1 (5.0)
Grade 3	2 (1.3)	1 (2.1)	0	0	2 (2.9)	1 (5.0)
Grade 4	5 (3.3)	1 (2.1)	2 (2.4)	1 (3.6)	3 (4.3)	0
Creatinine (μmol/L)						
Grade 1	4 (2.6)	1 (2.1)	2 (2.4)	1 (3.6)	2 (2.9)	0
Grade 2	7 (4.6)	1 (2.1)	4 (4.9)	1 (3.6)	3 (4.3)	0
Grade 3	2 (1.3)	1 (2.1)	0	0	2 (2.9)	1 (5.0)

Source: HPTN 077 CSR
Abbreviations: ALT, alanine aminotransferase; CAB, cabotegravir

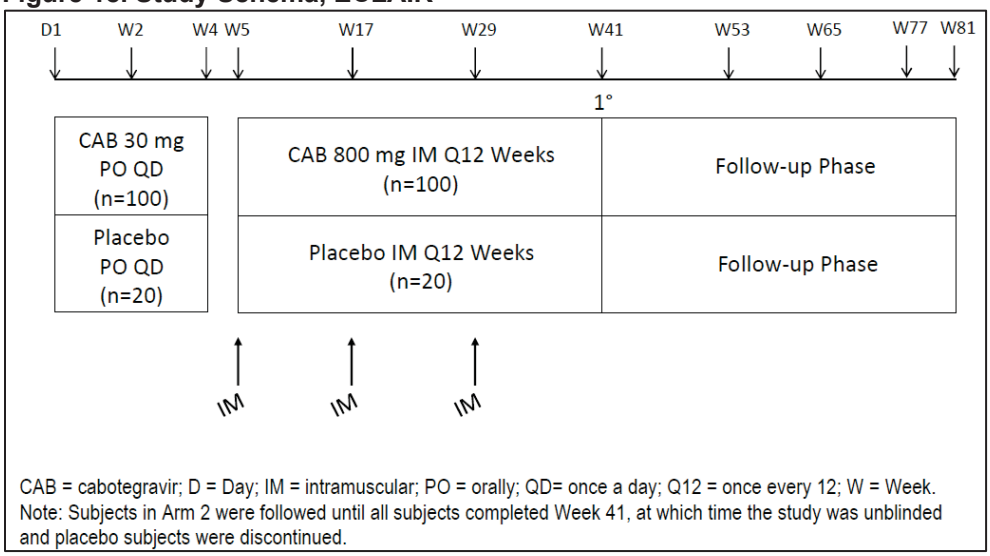
Weight gain at Week 41 was similar in the CAB and placebo group (the CAB treatment group had a median (min, max) weight gain of 1.10 (-13.3, 20.8) kg at Week 41 compared with 1.10 (-12.6, 64.2) kg in the placebo group.

Lastly, the AESI's of ISR, hypersensitivity reaction (HSR), and rash were reviewed, and the findings did not change the conclusions drawn based on the HPTN 083 and HPTN 084 data.

17.7.2. ÉCLAIR

The ÉCLAIR trial was a phase 2a study to evaluate the safety, tolerability and acceptability of CAB LA in HIV-1 uninfected men. The Study Design is depicted in Figure 18. Of note, at Week 41 the study was unblinded and subjects in the placebo group were discontinued. Participants in the CAB group were followed for 52 weeks after the last injection at Week 29 (i.e., through Week 81). The safety review presented below will focus on safety data through Week 41.

Figure 18. Study Schema, ECLAIR



CAB = cabotegravir; D = Day; IM = intramuscular; PO = orally; QD= once a day; Q12 = once every 12; W = Week.
Note: Subjects in Arm 2 were followed until all subjects completed Week 41, at which time the study was unblinded and placebo subjects were discontinued.

Source: ÉCLAIR CSR

As shown in Table 130, a greater proportion of CAB participants than placebo participants experienced ADRs. The majority of these were Grade 1-3 in severity, though two Grade 4 ADRs were reported among CAB participants (both were blood CPK increased AEs). The most common ADRs were local ISRs, followed by pyrexia, headache, and fatigue.

Table 130. Summary of Drug-Related Adverse Events in at Least 2 Subjects by Treatment Group, System Organ Class, and Maximum Toxicity for On-Treatment, ÉCLAIR Trial

Treatment Group System Organ Class Preferred Term	Maximum Toxicity				
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Placebo (N=21)					
Any event	9 (43)	6 (29)	0	0	15 (71)
General disorders and administration site conditions					
Any event	11 (52)	1 (5)	0	0	12 (57)
Injection site pain	11 (52)	1 (5)	0	0	12 (57)
Injection site pruritus	3 (14)	0	0	0	3 (14)
CAB (N=105)					
Any event	32 (30)	47 (45)	20 (19)	2 (2)	101 (96)
General disorders and administration site conditions					
Any event	35 (33)	38 (36)	18 (17)	0	91 (87)
Injection site pain	32 (30)	36 (34)	18 (17)	0	86 (82)
Injection site swelling	15 (14)	6 (6)	0	0	21 (20)
Injection site pruritus	12 (11)	6 (6)	0	0	18 (17)
Injection site warmth	10 (10)	2 (2)	0	0	12 (11)
Pyrexia	7 (7)	5 (5)	0	0	12 (11)
Fatigue	8 (8)	3 (3)	0	0	11 (10)
Injection site bruising	10 (10)	1 (<1)	0	0	11 (10)
Injection site induration	7 (7)	3 (3)	0	0	10 (10)
Chills	2 (2)	2 (2)	1 (<1)	0	5 (5)
Injection site erythema	5 (5)	0	0	0	5 (5)
Injection site discolouration	4 (4)	0	0	0	4 (4)
Malaise	1 (<1)	3 (3)	0	0	4 (4)
Nervous System Disorders					
Any event	16 (15)	4 (4)	0	0	20 (19)
Headache	10 (10)	2 (2)	0	0	12 (11)
Dizziness	3 (3)	1 (<1)	0	0	4 (4)
Somnolence	2 (2)	0	0	0	2 (2)
Gastrointestinal disorders					
Any event	13 (12)	3 (3)	0	0	16 (15)
Diarrhoea	8 (8)	1 (<1)	0	0	9 (9)
Abdominal discomfort	1 (<1)	1 (<1)	0	0	2 (2)
Abdominal distension	2 (2)	0	0	0	2 (2)
Investigations					
Any event	5 (5)	6 (6)	0	2 (2)	13 (12)
Blood CPK increased	0	3 (3)	0	2 (2)	5 (5)
Alanine aminotransferase increased	3 (3)	0	0	0	3 (3)
Aspartate aminotransferase increased	2 (2)	1 (<1)	0	0	3 (3)
White blood cell count decreased	3 (3)	0	0	0	3 (3)

Continued

Table 130, continued

Treatment Group System Organ Class Preferred Term	Maximum Toxicity				
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Neutrophil count decreased	2 (2)	0	0	0	2 (2)
Blood and lymphatic system					
Any event	2 (2)	5 (5)	2 (2)	0	9 (9)
Neutropenia	3 (3)	4 (4)	1 (<1)	0	8 (8)
Musculoskeletal and connective tissue disorders					
Any event	3 (3)	3 (3)	1 (<1)	0	7 (7)
Myalgia	3 (3)	2 (2)	1 (<1)	0	6 (6)
Metabolism and nutritional disorders					
Any event	3 (3)	1 (<1)	0	0	4 (4)
Decreased appetite	2 (2)	1 (<1)	0	0	3 (3)
Skin and subcutaneous tissue disorders					
Any event	1 (<1)	2 (2)	1 (<1)	0	4 (4)
Hyperhidrosis	1 (<1)	1 (<1)	0	0	2 (2)

Source: ÉCLAIR CSR

Seven (6.7%) CAB participants and one (4.8%) placebo subject experienced an AE that led to treatment discontinuation. All of the AEs leading to discontinuation among the CAB participants occurred during the OLI and were nonserious (neutropenia, n=3; blood CPK increased, n=3; fatigue, n=1). Of note, the neutropenia AEs were Grade 2 (n=2) and Grade 3 (n=1) in severity and all three neutropenia AEs were assessed to be treatment related. Please refer to Section 7.6.3.11 for a detailed discussion of neutropenia events across the CAB for HIV-1 PrEP development program.

There were no deaths in the ÉCLAIR trial. There were two SAEs, one in the CAB group and one in the placebo group. The SAE reported by a CAB participant was a Grade 3 appendicitis event occurring 96 days after the most recent CAB dose. The event was not assessed to be drug-related and no action was taken with the study drug.

Review of the mean changes from baseline in chemistry and hematology laboratory parameters revealed that there was a greater increase in mean ALT, AST, and creatinine kinase values among CAB participants compared to placebo participants. Notably, no difference in the mean change in neutrophil count from baseline across arms was reported. Treatment-emergent neutrophil abnormalities are summarized in Table 131. Of note, one CAB participant had a Grade 4 neutrophil abnormality.

Table 131. Summary of Maximum Treatment-Emergent Neutrophil Abnormalities, ECLAIR Trial

Laboratory Parameter Grade	CAB Oral Phase N=105 n (%)	Placebo Oral Phase N=21 n (%)	CAB Injection Phase N=21 n (%)	TDF/FTC Injection Phase N=21 n (%)
Neutrophils				
Grade 1	3 (3)	0	8 (9)	2 (10)
Grade 2	1 (<1)	0	1 (1)	0
Grade 3	0	0	0	0
Grade 4	1 (<1)	0	0	0

Source: ÉCLAIR CSR
Abbreviations: CAB, cabotegravir; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Grade 3 and 4 laboratory abnormalities were more common in the CAB arm and were largely CPK and lipase abnormalities. A summary of all Grade 3 and 4 laboratory abnormalities is provided in Table 132.

Table 132. Subjects With Grade 3 or Grade 4 Laboratory Abnormalities, ÉCLAIR Trial

Treatment	Subject	Lab test (unit)	Visit (week)	Value	Grade	Normal Range
Placebo	(b) (6)	CPK (IU/L)	18	3230	3	0-235
		APTT (standard)	41	>18	4	0.9-1.1
		PT (sec)	41	>200	4	9-11.5
CAB		CPK (IU/L)	41	3146	3	0-235
		CPK (IU/L)	41 (FU)	4952	4	0-235
		CPK (IU/L)	18	2489	3	0-235
		CPK (IU/L)	17	9031	4	0-235
		CPK (IU/L)	4	6549	4	0-235
		CPK (IU/L)	Oral FU	5017	4	0-235
		CPK (IU/L)	4	8741	4	0-235
		CPK (IU/L)	4	19761	4	0-235
		Lipase (U/L)	2	228	3	7-60
		Lipase (U/L)	5	219	3	7-60

Treatment	Subject	Lab test (unit)	Visit (week)	Value	Grade	Normal Range
	(b) (6)	Lipase (U/L)	4	183	3	7-60
		Lipase (U/L)	9	190	3	7-60
		Lipase (U/L)	13	183	3	7-60
		AST (IU/L)	4	677	4	0-42
		Neutrophils (GI/L)	4	0.47	4	1.8-8
		Leukocytes (GI/L)	6	1.8	2	3.8-10.8
		Glucose (mmol/L)	4	1.7	3	3.9-5.5

Source: ÉCLAIR CSR
Abbreviations: CAB, cabotegravir

In conclusion, the majority of the potential safety concerns identified in this trial are discussed in detail in Section 7.6 and are being addressed through labeling.

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Narratives for *Infected Subjects Assigned to Receive CAB LA*

Four subjects from HPTN 083, Subjects [redacted] (A1), [redacted] (A4), [redacted] (A3), and [redacted] (A2), and one subject from HPTN 084, Subject [redacted] were determined retrospectively to have been infected at enrollment (Day 1). These individuals were acutely infected at the time of the enrollment visit and were within the eclipse phase of HIV-1 diagnostic assays used to test for infection at the local clinical sites (i.e., the rapid tests and Ag/Ab assays).

- HPTN 083 Subject [redacted] (A1) is from Latin America and infected by HIV-1 subtype B. No CAB LA injections were administered. HIV-1 infection was detected by the local site's Ag/Ab test on Day 29, when plasma CAB concentrations were 3.228 mcg/mL, and retrospectively by the central laboratory's qualitative and quantitative RNA assays on Day 1. The viral load on Day 1 was 4,010 c/mL and had decreased to 78 c/mL by Day 29. No HIV-1 with INSTI resistance-associated substitutions (RAS) were detected by genotypic analysis of the Day 1 sample; phenotyping was not successful. The last time point assessed was Day 42, at which time RNA was not detected (i.e., below the assay's lower limit of quantification and analyte not detected). ART was not started at the time of the data cutoff, Day 338. No samples for genotyping were collected following the cessation of oral CAB and viral rebound, which may have been an optimal time for detecting any CAB-resistant virus.
- HPTN 083 Subject [redacted] (A4) is from Latin America and infected by HIV-1 subtype B. CAB LA injections were administered on Days 39 and 64. The infection was detected by the local site's Ag/Ab assay on Day 64, at which time the plasma CAB concentration was 2.997 mcg/mL, and retrospectively by the central laboratory's qualitative RNA, quantitative RNA, and Ag/Ab assays on Day 1. The viral load on Day 1 was 44,180 c/mL and was the only assessed time point with a viral load sufficient for resistance analyses. No INSTI RAS were detected in virus from that sample, and phenotyping indicated susceptibility to CAB (1.2-fold reduction in susceptibility relative to reference). ART (lamivudine/tenofovir disoproxil fumarate/ritonavir-boosted darunavir (3TC/TDF/DRVr)) was started on Day 99 while viral loads remained below 500 c/mL. No samples with viral loads permitting resistance analyses of virus collected after CAB administration were collected after Day 1 through Day 432, the last time point assessed. Interestingly, no viral analytes were detected by the central laboratory's assays, including by the RNA-specific assays, during several intermittent time points before ART was started (Days 31, 39, 64, and 71), presumably due to virologic suppression by CAB monotherapy.
- HPTN 083 Subject [redacted] (A3; also referred to as A3/D5) is from Latin America and infected by HIV-1 subtype B. CAB LA injections were received on Days 36 and 66. The infection was detected by the local site's Ag/Ab test on Day 73, when the plasma CAB concentration was 5.428 mcg/mL, and retrospectively by the central laboratory's qualitative and quantitative RNA assays, but not by the Ag/Ab assay, on Day 1. Viral loads were 1,360 c/mL, 1,440 c/mL, and 76,090 c/mL on Days 1, 186, and 249,

respectively; plasma CAB concentrations on Days 186 and 249 were 0.586 and 0.056 mcg/mL, respectively. No INSTI RAS were detected from samples collected at these 3 time points, and phenotyping indicated susceptibility to CAB (0.64-, 0.52-, and 0.74-fold reductions in susceptibility relative to reference, respectively). ART was not started by the time of the data cutoff, Day 347. According to Marzinke and colleagues (Marzinke et al. 2021), ART (TDF/FTC/efavirenz (EFV)) was started 6 months after the last on-study virology assessment (Day 249) and viral load was measured at 142 c/mL after 1 month on ART. Interestingly, the infection was only detected intermittently until Day 186, at which time plasma CAB concentrations had dropped to 0.586. Virus was detected only intermittently in samples collected between Days 29 through 117, presumably due to virologic suppression by CAB monotherapy. All the central laboratory's diagnostic tests were negative on Days 29, 36, 66, 73, 82, and 117, although the local site's Ag/Ab assay was positive on Days 73 and 82, but negative again on Day 117.

- HPTN 083 Subject (b) (6) (A2) is from Latin America and infected by HIV-1 subtype C. A CAB LA injection was administered on Day 41. The infection was detected by the local site's Ag/Ab test on Day 61 and retrospectively by the central laboratory's qualitative and quantitative RNA assays, but not by the Ag/Ab assay, on Day 1. Viral loads were at 50,080 c/mL on Day 1, fell to a low of 204 c/mL on Day 41, when the plasma CAB concentration was 3.318 mcg/mL, and rebound to 1,660 c/mL and 4,829 c/mL on Days 61 and 70, respectively. Plasma CAB concentrations remained high at Days 61 and 70, at 3.840 and 2.553 mcg/mL, respectively. No variants expressing INSTI RAS were detected in samples collected on Days 1, 20, or 30, but viruses expressing E138K + Q148K were detected in the Day 61 and Day 70 samples. Attempts to phenotypically characterize this variant were unsuccessful. An unspecified ART regimen was started on Day 114; according to Marzinke and colleagues (Marzinke et al. 2021), the ART regimen was 3TC/TDF/ DRVr and successfully suppressed viral replication.
- HPTN 084 Subject (b) (6) is from Uganda and infected by HIV-1 subtype A1. CAB LA injections were administered on Days 33, 60, 114, 173, and 227. The infection was detected by the local site's Ag/Ab assay on Day 227 and retrospectively by the central laboratory's qualitative and quantitative RNA assays, but not by the Ag/Ab assay, on Day 1. Viral loads were <40 c/mL on Day 1, increased to 6,300 c/mL by Day 33, when the plasma CAB concentration was below the assay's lower limit of quantification (BLQ; <0.025 mcg/mL), and then dropped to 87 c/mL on Day 38, when the plasma CAB concentration was 0.557 mcg/mL. No variants expressing INSTI RAS were detected in samples collected on Days 15, 26, or 33. ART was not started by the time of the data cutoff, Day 410. The infection was undetected by any of the employed assays (Ag/Ab or qualitative RNA) between Days 60 and 173, presumably due to viral suppression by CAB monotherapy. Although the infection was detected by the central laboratory's qualitative RNA assay between Days 1 and 38, RNA was not detected in samples collected between Days 60 and 401, when plasma CAB concentrations varied between 0.701 and 3.853 mcg/mL, although the central laboratory's Ag/Ab assay was able to detect infection between Days 227 and 401; the central laboratory's confirmatory Ab test produced indeterminate results during this period.

Six subjects from HPTN 083, Subjects [redacted] (B4), [redacted] (C2), [redacted] (B5), [redacted] (B1), [redacted] (B2), and [redacted] (B3), and three subjects from HPTN 084, Subjects [redacted], and [redacted] were infected during periods when CAB plasma concentrations were below those expected for individuals compliant with recommended use (i.e., 0.65 mcg/mL) at the time of HIV-1 diagnosis.

- HPTN 083 Subject [redacted] (B4) is from the United States and infected by HIV-1 of an unknown subtype. CAB LA injections were administered on Days 37, 62, and 120. The infection was identified by both the local site's rapid tests and Ag/Ab assay and by the central laboratory's Ag/Ab, Ab, qualitative RNA, and quantitative RNA assays on Day 401, when the plasma CAB concentration had fallen to below the assay's lower limit of quantification. The last negative HIV-1 diagnosis was on Day 338, when the plasma CAB concentration was 0.099 mcg/mL. ART (emtricitabine/tenofovir alafenamide/bictegravir (FTC/TAF/BIC)) was started on Day 391; although it is unclear why ART was started before the infection was diagnosed. Viral loads were 770 c/mL and 410 c/mL on Days 401 and 407, respectively, no RNA was detected on Day 436, and RNA was detected but <40 c/mL on Day 478. Attempts to genotypically and phenotypically characterize virus were unsuccessful. According to Marzinke and colleagues (Marzinke et al. 2021), this individual had a viral load of 26 c/mL 5 months after beginning ART.
- HPTN 083 Subject [redacted] (C2) is from Latin America and infected by HIV-1 subtype BF. No CAB LA injections were administered. The infection was identified by the local site's rapid test and Ag/Ab assay on Day 232 and retrospectively by the central laboratory's qualitative and quantitative RNA, but not Ag/Ab assay, on Day 47; there were no intervening assessments. The viral load on Day 47 was 494 c/mL, while those on Days 232 and 233 were 229,810 c/mL and 207,810 c/mL, respectively. Plasma CAB concentrations were quantifiable only on Day 233, at 2.559 mcg/mL. No HIV-1 expressing INSTI RAS were detected in samples collected on Days 232 and 233. ART (TDF/FTC/EFV) was started on Day 234.
- HPTN 083 Subject [redacted] (B5) is from the United States and infected by HIV-1 subtype B. No CAB LA injections were administered. The infection was detected by the local site's Ag/Ab assays and by the central laboratory's Ag/Ab, Ag, qualitative RNA, and quantitative RNA assays on Day 350, when the plasma CAB concentration was below the assay's lower limit of quantification. The last negative diagnosis was on Day 34, when the plasma CAB concentration was 1.565 mcg/mL; there were no intervening assessments. The viral load on Day 350 was 2,559 c/mL, when the plasma CAB concentration was BLQ. No HIV-1 expressing INSTI RAS was detected in the Day 350 sample. ART (FTC/TAF/BIC) was started on Day 350. According to Marzinke and colleagues (Marzinke et al. 2021), the viral load was <20 c/mL 1 month later.
- HPTN 083 Subject [redacted] (B1) is from the United States and infected by HIV-1 subtype B. CAB LA injections were administered on Days 39 and 108. Infection was detected by the local site's rapid test and Ag/Ab assay and by the central laboratory's Ag/Ab, Ab, qualitative RNA, and quantitative RNA assays on Day 957, when the plasma CAB concentration was 0.065 mcg/mL. The last negative diagnosis was on Day 585, when the plasma CAB concentration was 0.154 mcg/mL; there were no intervening

assessments. Viral loads were 65,530 c/mL and 46,230 c/mL on Days 957 and 960, respectively. No HIV-1 expressing INSTI RAS was detected in the Day 957 sample. ART was started on Day 957. According to Marzinke and colleagues (Marzinke et al. 2021), the regimen was FTC/TAF/DRVc (cobicistat-boosted darunavir) and the viral load was 608 c/mL 3 months later.

- HPTN 083 Subject (b) (6) (B2) is from Asia and infected by HIV-1 subtype A/B. No CAB injections were administered. Infection was detected by the local site's rapid tests and Ag/Ab assay and by the central laboratory's Ag/Ab, Ab, qualitative RNA, and quantitative RNA assays on Day 725. The last negative diagnosis was on Day 388; there were no intervening assessments. Plasma CAB concentrations were < 0.025 mcg/mL at all time points. A viral load of 53,220 c/mL was measured on Day 725. No virus expressing INSTI RAS was detected in the Day 725 sample. ART (TDF/FTC/EFV) was started on Day 726. The regimen was switched to TDF/FTC/RPV on Day 907. According to Marzinke and colleagues (Marzinke et al. 2021), the viral load was <20 c/mL after 5 months on ART.
- HPTN 083 Subject (b) (6) (B3) is from Asia and infected by HIV-1 subtype A/E. CAB LA injections were administered on Days 36, 80, 128, and 176. Infection was detected by the local site's rapid test and Ag/Ab assay and by the central laboratory's Ag/Ab, qualitative RNA, and quantitative RNA assays on Day 393, when the plasma CAB concentration was 0.100 mcg/mL. The last negative diagnosis was on Day 194, when the plasma CAB concentration was 7.674 mcg/mL; there were no intervening assessments. Viral loads of 50,440 c/mL and 93,510 c/mL were measured on Days 393 and 396, respectively. No virus expressing INSTI RAS was detected in the Day 393 sample. ART (3TC/TDF/EFV) was started on Day 396.
- HPTN 084 Subject (b) (6) is from Zimbabwe and infected by HIV-1 subtype C. No CAB LA injections were administered. Infection was detected by the local site's rapid tests and Ag/Ab assay and by the central laboratory's Ag/Ab, qualitative RNA, and quantitative assay on Day 402, when the plasma CAB concentrations were < 0.025 mcg/mL. The last negative diagnosis was on Day 275, when the plasma CAB concentration was < 0.025 mcg/mL; there were no intervening assessments. Viral loads of 42,810 c/mL, 32,720 c/mL, and 44,870 c/mL were measured on Days 402, 403, and 535; plasma CAB concentrations were < 0.025 mcg/mL at all three time points. Genotyping was conducted on samples collected on Days 402 and 535; no virus expressing INSTI RAS was detected. No ART was started by the time of the data cutoff, Day 550.
- HPTN 084 Subject (b) (6) is from South Africa and infected by HIV-1 subtype C. No CAB LA injections were administered. Infection was detected by the local site's rapid tests and Ag/Ab assay and by the central laboratory's Ag/Ab, Ab, qualitative RNA, and quantitative RNA assays on Day 77, when the plasma CAB concentration was < 0.025 mcg/mL. The last negative diagnosis was on Day 26, when the plasma CAB concentration was < 0.025 mcg/mL. Viral loads of 26,840 c/mL and 31,420 c/mL were measured on Days 77 and 78, respectively. Genotyping was conducted on samples collected on Day 77; no virus expressing INST RAS was detected. No ART was started by the time of the data cutoff, Day 462.

- HPTN 084 Subject [redacted] is from South Africa and infected by HIV-1 subtype C. Infection was detected by the local site and central laboratories on Day 522. CAB LA injections were administered on Days 39, 79, 109, 169, 211, 317, 351, 409, and 522. Plasma CAB concentrations were 0.416 mcg/mL at the time of HIV-1 diagnosis (Day 522) but CAB concentration data were missing for the preceding visit (Day 409). Plasma CAB concentrations were 2.722 mcg/mL at the next preceding visit (Day 351). Viral loads were 875,200 c/mL, 3,927,990 c/mL, <40 c/mL, <40 c/mL, not detected, and not detected on Days 522, 526, 604, 710, 814, and 900, respectively. Genotyping was conducted on samples collected on Days 522 and 526. No virus expressing INSTI RAS was detected. No phenotyping was attempted. ART was not started at the time of the data cutoff, Day 976.

***Reviewer's Note**: Subject [redacted] was diagnosed with an HIV-1 infection after experiencing a 113-day gap between the Day 409 and Day 522 injections. The plasma CAB concentration was 0.416 mcg/mL during the Day 522 visit, at which time the HIV-1 infection was first diagnosed. This infection can likely be attributed to inadequate CAB concentrations if the infection occurred after ~Day 470 when the PK target may not have been maintained. However, this case could represent another pharmacologic failure if the infection occurred closer to the Day 409 injection when CAB concentrations are expected to have been above the target PK threshold.*

Six subjects from HPTN 083 represent potential pharmacologic failures. These include Subjects [redacted] (D4), [redacted] (D3), [redacted] (D2), and [redacted] (D1), who became infected despite receiving the scheduled CAB LA injections, and Subjects [redacted] (C1) and [redacted] (C3), who became infected during the OLI despite having achieved target plasma CAB concentrations ≥0.65 mcg/mL at the time of diagnosis.

- HPTN 083 Subject [redacted] (D4) is from South Africa and infected by HIV-1 subtype C. CAB LA injections were administered on Days 36, 64, 120, and 178. Infection was detected by the local site's Ag/Ab test on Day 178, when the plasma CAB concentration was 1.930 mcg/mL, and by the central laboratory's qualitative and quantitative RNA assays on Day 133, when the plasma CAB concentration was 2.017 mcg/mL. The last negative diagnosis was on Day 120, when the plasma CAB concentration was 1.369 mcg/mL. Interestingly, CAB plasma concentrations were ≤0.65 mcg/mL, at 0.389 mcg/mL and 0.305 mcg/mL on Days 43 and 64, respectively, despite receiving a CAB LA injection on Day 36. Viral loads were <40 c/mL (RNA detected but below the assay's lower limit of quantification, 40 c/mL), 158 c/mL, 263 c/mL, 152,730 c/mL on Days 133, 178, 182, and 274, respectively. ART (FTC/TDF/EFV) was started on Day 274 and viral loads were <40 c/mL on Days 358 and 443. Genotyping was conducted on the Day 274 sample, when the plasma CAB concentration was 2.261 mcg/mL, and virus expressing G140A+Q148R was detected. Phenotyping indicated that this variant has a 13-fold reduction in susceptibility to CAB.
- HPTN 083 Subject [redacted] (D3) is from Latin America and infected by HIV-1 subtype B/F. CAB LA injections were administered on Days 37, 64, 120, 182, and 232. Infection was detected by the local site's rapid test on Day 237 (an indeterminant result was produced for the Ag/Ab assay on Day 232), when the plasma CAB concentration was 1.645 mcg/mL, and retrospectively by the central laboratory's qualitative and quantitative RNA assays, but not the Ag/Ab assay, on Day 120, when the plasma CAB

concentration was 1.504 mcg/mL. The plasma CAB concentration at the last HIV-1 negative visit (Day 76) was 3.046 mcg/mL. Timepoints with viral loads >500 c/mL were Days 120, 232, and 237, with viral loads of 860 c/mL, 7,160 c/mL, and 5,510 c/mL, respectively. No virus expressing INSTI RAS was detected in the Day 120 sample, while an R263K-expressing virus was detected in the Day 232 and 237 samples. Phenotyping indicated that the variant in the Day 237 sample had a 2.32-fold reduction in CAB susceptibility. ART (3TC/TDF/DRVr) was started on Day 237. According to Marzinke and colleagues (Marzinke et al. 2021), virus was suppressed after 1 month on ART.

- HPTN 083 Subject (b) (6) (D2) is from Latin America and infected by HIV-1 of an unknown subtype. CAB LA injections were administered on Days 36, 64, 120, 176, 232, and 288. Infection was detected by the local site's Ag/Ab assay on Day 288, when the plasma CAB concentration was 1.795 mcg/mL, and by the central laboratory's qualitative RNA, but not by the Ag/Ab or quantitative RNA assay, on Day 190, when the plasma CAB concentration was 1.405 mcg/mL. The plasma CAB concentration was 1.353 mcg/mL at the last HIV-1 negative visit (Day 176). Viral RNA was not detected on Day 190, but was 245 c/mL on Day 470, and <40 c/mL on Day 523. The plasma CAB concentration on Day 523, the last assessed time point, was 0.491 mcg/mL. ART was not started by the time of the data cutoff, Day 553.
- HPTN 083 Subject (b) (6) (D1) is from the United States and infected by HIV-1 of an unknown subtype. CAB LA injections were administered on Days 34, 62, 118, 174, 225, 300, 337, 393, 449, and 505. Infection was detected by the local site's Ag/Ab test on Day 505, when the plasma CAB concentration was 1.444 mcg/mL, and by the central laboratory's qualitative and quantitative RNA assays Day 393, when the plasma CAB concentration was 1.613 mcg/mL. The plasma CAB concentration at the last HIV-1 negative visit (Day 351) was 2.320 mcg/mL. Viral loads were quantifiable on Days 393, 407, 449, and 470, at 130 c/mL, 163 c/mL, 87 c/mL, and 71 c/mL, respectively. Viral loads were <40 c/mL on Days 505 and 510, when the plasma CAB concentration was 2.151 mcg/mL, and at which point ART (FTC/TAF/DRVc) was started. Viral RNA was not detected on Days 585 and 984.
- HPTN 083 Subject (b) (6) (C1) is from Latin America and infected by HIV-1 subtype B. Infection was detected by the local site on Day 75 and retrospectively by the central laboratory on Day 28. CAB LA injections were administered on Days 37 and 65. Plasma CAB concentrations were 6.301 mcg/mL at the earliest HIV-1 diagnosis (Day 28) and 4.013 mcg/mL at the preceding visit (Day 17). Viral loads were 120 c/mL, 161 c/mL, 137 c/mL, 2,174 c/mL, 1,373 c/mL, and 2,549 c/mL on Days 28, 37, 45, 65, 75 and 79, respectively. Genotyping was conducted on samples collected on Days 65, 79, and 79. Virus expressing L74I+Q148R+E157Q was detected in the Day 65 sample and virus expressing L74I+E138E/K+G140G/S+Q148R+E157Q in the Day 75 and 79 samples. Phenotyping these variants was unsuccessful. No ART was started by the time of the data cutoff, Day 569.
- HPTN 083 Subject (b) (6) (C3) is from Latin America and infected by HIV-1 subtype B. A CAB LA injection was administered on Day 35. Infection was detected by the local site's rapid tests and Ag/Ab assay on Day 55, when the plasma CAB concentration was 1.108 mcg/mL, and by the central laboratory's qualitative RNA assay

on Day 20, when the plasma CAB concentration was 10.690 mcg/mL. Viral loads were quantifiable on Days 41, 55, 56 and 142 at 99 c/mL, 102,329 c/mL, 218,776 c/mL, and 375 c/mL, respectively. ART (TDF/FTC/EFV) was started on Day 65, after which time viral loads were 375 c/mL, <40 c/mL, and then not detected on Days 142, 225, and 337/384, respectively. Genotyping was conducted on samples collected on Days 55 and 56. Virus expressing E138A+Q148R was detected. Phenotyping indicated that the Day 55 and 56 variants were 5.92- and 7.42-fold less susceptible to CAB, respectively.

Table 133. Diagnostic and Virology Data for HIV-1 Infections Among Subjects Assigned to the CAB Arms, Trials HPTN 083 and HPTN 084

			Site Diagnostics						Central					
			Rapid Tests		Ag/Ab Tests		HIV-1 RNA[4]		Ag/		HIV-1 RNA[4]			
Subject (Code)[1]	Day[2]	CAB[3] (mcg/mL)	1	2	1	2	Qual	(c/mL)	Ab	Ab	Qual	(c/mL)	ST[5]	INSTI RAS[6]
HPTN 083														
(b) (6)	-13										-			
(A1)	1	<0.025	-		-				-		+	4,010	B	WT
	15	6.580	-		-				-		+	<40		
	29	3.228	-		+	-		50	-		+	78		
	42	3.736	-		+	-		54	-		+	<40		
(b) (6)	1	<0.025	-		-				+	-	+	44,180	B	WT
(A4)	18	5.587	-		-				-		+	<40		
	31	4.964	-		-				-		-			
	39	2.636	-		-				-		-			
	46	2.113	-		-				-		+	<40		
	64	2.997	-		+				-	-	-			
	71	4.901	-		+				+	-	-			
	99	3.090	-		-				-		-			
	165	0.800							-		-			
	179	0.769	-						-		-			
	267	0.151							-		-			
	341	0.031							-		-			
	432	<0.025							-		-			
(b) (6)	1	<0.025	-		-				-			ND		
(C1)	17	4.013	-		-				-		-			
	28	6.301	-		-				-		+	120		
	37	1.839	-		-				-		+	161		
	45	1.219	-		-				-		+	137		
	65	1.841	-		-				-		+	2,174	B	L74I, Q148R, E157Q
	75	3.469	-		+			1139	+	-	+	1,373	B	L74I, E138E/K, G140G/S, Q148R, E157Q
	79	3.647	-		+	-		1911	-	-	+	2,549	B	L74I, E138E/K, G140G/S, Q148R, E157Q

			Site Diagnostics						Central					
			Rapid Tests		Ag/Ab Tests		HIV-1 RNA[4]		Ag/		HIV-1 RNA[4]			
Subject (Code)[1]	Day[2]	CAB[3] (mcg/mL)	1	2	1	2	Qual	(c/mL)	Ab	Ab	Qual	(c/mL)	ST[5]	INSTI RAS[6]
(b) (6)	1	<0.025	-		-				-		-			
(B4)	17	0.047	-		-						-			
	29	<0.025	-		-						-			
	37	<0.025	-		-						-			
	45	4.644	-		-						-			
	62	2.965	-		-						-			
	69	8.105	-		-						-			
	120	1.205	-		-						-			
	133	1.722	-		-						-			
	164	1.589	-		-				-		-			
	246	0.648	-		-				-		-			
	338	0.099	-		-				-		-			
	401	<0.025	+		+			828	+	+	+	770		
	407	<0.025	+		+			244	+	+	+	410		
	436	<0.025										ND		
	478	<0.025			+		+	26				<40		
(b) (6)	1	<0.025	-		-				-		-			
(D4)	15	4.156	-		-						-			
	30	3.570	-		-						-			
	36	4.061	-		-						-			
	43	0.389	-		-						-			
	64	0.305	-		-				-		-			
	71	1.091	-		-				-		-			
	120	1.369	-		-				-		-			
	133	2.017	-		-				-		+	<40		
	178	1.930	-		+		+	174	+	±	+	158		
	182	3.156	-		+		-	298	+	±	+	263		
	274	2.261							+	+	+	152,730	C	G140A, Q148R
	358	0.238							+	+	+	<40		
	443	0.057							+	+	+	<40		

			Site Diagnostics						Central					
			Rapid Tests		Ag/Ab Tests		HIV-1 RNA[4]		Ag/		HIV-1 RNA[4]			
Subject (Code)[1]	Day[2]	CAB[3] (mcg/mL)	1	2	1	2	Qual	(c/mL)	Ab	Ab	Qual	(c/mL)	ST[5]	INSTI RAS[6]
(b) (6)	1	<0.025	-	-	-				-		-			
(C3)	20	10.690	-	-	-				-		+	ND		
	28	8.767	-	-	-				-		+	<40		
	35	4.488	-	-	-				-		-	ND		
	41	1.582	-	-	-				-		+	99		
	55	1.108	+	+	+				+	±	+	102,329	B	E138A, Q148R
	56	1.182	+	+	+			379978	+	+	+	218,776	B	E138A, Q148R
	142	0.571										375		
	225	0.126										<40		
	337	<0.025										ND		
	384	<0.025										ND		
(b) (6)	1	<0.025	-		-				-		-			
(D3)	15	3.814	-		-						-			
	29	4.346	-		-						-			
	37	3.505	-		-						-			
	43	0.767	-		-				-		-			
	64	0.953	-		-				-		-			
	76	3.046	-		-				-		-			
	120	1.504	-		-				-		+	860	BF	WT
	169	1.538	-		-				-		+	ND		
	182	1.213	-		-				-		+	<40		
	196	1.848	-		-				-		+	112		
	232	1.220	-		±				+	-	+	7,160	BF	R263K
	237	1.645	+		±			4628	+	±	+	5,510	BF	R263K

Subject (Code)[1]	Day[2]	CAB[3] (mcg/mL)	Site Diagnostics: Rapid Tests 1	Site Diagnostics: Rapid Tests 2	Site Diagnostics: Ag/Ab Tests 1	Site Diagnostics: Ag/Ab Tests 2	Site Diagnostics: HIV-1 RNA[4] Qual	Site Diagnostics: HIV-1 RNA[4] (c/mL)	Central: Ag/Ab	Central: Ab	Central: HIV-1 RNA[4] Qual	Central: HIV-1 RNA[4] (c/mL)	ST[5]	INSTI RAS[6]
(b) (6)	1	<0.025	-		-				-		+	1,360	B	WT
(A3)	15	8.867	-		-				+	-	+	<40		
	29	10.180	-		-				-		-			
	36	11.210	-		-				-		-			
	43	8.424	-		-				-		+	ND		
	66	1.383	-		-				-		-			
	73	5.428	-		+				-		-			
	82	3.370	-		+				-		-			
	117	2.724	-		-				-		-			
	186	0.586							+	±	+	1,440	B	WT
	249	0.056							+	+	+	76,090	B	WT
(b) (6)	1	<0.025	-		-				-		-			
(C2)	26	<0.025	-		-				-		-			
	47	<0.025	-		-				-		+	494		
	232	<0.025	+		+			574,646	+	+	+	229,810	BF	WT
	233	2.559	+		+			326,823	+	+	+	207,810	BF	WT

Subject (Code)[1]	Day[2]	CAB[3] (mcg/mL)	Site Diagnostics: Rapid Tests 1	Site Diagnostics: Rapid Tests 2	Site Diagnostics: Ag/Ab Tests 1	Site Diagnostics: Ag/Ab Tests 2	Site Diagnostics: HIV-1 RNA[4] Qual	Site Diagnostics: HIV-1 RNA[4] (c/mL)	Central: Ag/Ab	Central: HIV-1 RNA[4] Ab	Central: HIV-1 RNA[4] Qual	Central: HIV-1 RNA[4] (c/mL)	ST[5]	INSTI RAS[6]
(b) (6)	1	<0.025	-		-				-		-			
(D2)	15	7.381	-		-						-			
	29	6.363	-		-						-			
	36	6.565	-		-						-			
	43	2.131	-		-						-			
	64	1.350	-		-						-			
	71	3.330	-		-						-			
	120	1.797	-		-				-		-			
	134	2.127	-		-				-		-			
	176	1.353	-		-				-		-			
	190	1.405	-		-				-		+	ND		
	232	1.175	-		-				-		-			
	245	3.207	-		-				-		+	ND		
	288	1.795	-		+				-		-			
	295	2.674	+		+				+	-	-			
	302	2.305	-		+				+	-	-			
	309	2.138	-		+				-		-			
	322	2.193	-		+				+	±	-			
	385	1.678	+	+	+		+		-		-			
	425	0.987	-		+				+	±	-			
	470	0.703	-		+	-		23	+	-	+	<40		
	523	0.491	+		+			23	+	±	+	<40		
(b) (6)	-13								-		-			
(A2)	1	<0.025	-		-				-		+	50,080	C	WT
	20	11.950	-		-				-		+	20,760	C	WT
	30	4.274	-		-				-		+	700	C	WT
	41	3.318	-		-				-		+	204		
	61	3.840	-		+				+	+	+	1,660	C	E138K, Q148K
	70	2.533	-		+	+		10,000	+	+	+	4,829	C	E138K, Q148K
(b) (6)	1	<0.025	-		-				-		-			
(B5)	13	<0.025	-		-				-		-			
	34	1.565	-		-				-		-			
	350	<0.025			+	+		3,300	+	+	+	2,559	B	WT

			Site Diagnostics						Central					
			Rapid Tests		Ag/Ab Tests		HIV-1 RNA[4]		Ag/		HIV-1 RNA[4]			
Subject (Code)[1]	Day[2]	CAB[3] (mcg/mL)	1	2	1	2	Qual	(c/mL)	Ab	Ab	Qual	(c/mL)	ST[5]	INSTI RAS[6]
(b) (6)	1	<0.025	-		-				-		-			
(D1)	15	7.112	-		-						-			
	27	5.847	-		-						-			
	34	4.342	-		-						-			
	41	0.742	-		-						-			
	62	1.613	-		-						-			
	69	2.210	-		-						-			
	118	1.986	-		-						-			
	139	1.889	-		-						-			
	174	2.104	-		-						-			
	188	1.995	-		-						-			
	225	1.409	-		-						-			
	239	1.966	-		-						-			
	300	1.218	-		-						-			
	306	1.848	-		-				-		-			
	337	2.468	-		-				-		-			
	351	2.320	-		-				-		-			
	393	1.613	-		-				-		+	130		
	407	2.251	-		-				-		+	163		
	449	1.696	-		-				-		+	87		
	470	2.514	-		-				-		+	71		
	505	1.444	-		+				+	+	+	<40		
	510	2.151			+	+	+	48	+	+	+	<40		
	585	1.551										ND		
	904	0.057										ND		

Subject (Code)[1]	Day[2]	CAB[3] (mcg/mL)	Site Diagnostics: Rapid Tests 1	Site Diagnostics: Rapid Tests 2	Site Diagnostics: Ag/Ab Tests 1	Site Diagnostics: Ag/Ab Tests 2	Site Diagnostics: HIV-1 RNA[4] Qual	Site Diagnostics: HIV-1 RNA[4] (c/mL)	Central: Ag/Ab	Central: Ab	Central: HIV-1 RNA[4] Qual	Central: HIV-1 RNA[4] (c/mL)	ST[5]	INSTI RAS[6]
(b) (6)	1	<0.025	-		-				-		-			
(B1)	18	8.703	-		-						-			
	32	10.970	-		-						-			
	39	7.695	-		-				-		-			
	45	2.341	-		-				-		-			
	101		-		-		-							
	108	0.907	-		-				-		-			
	206		-		-									
	214	1.176	-		-				-		-			
	313	0.727	-		-				-		-			
	373	0.491	-		-				-		-			
	515	0.204							-		-			
	585	0.154	-		-				-		-			
	957	0.065	+		+			103,000	+	+	+	65,530	B	WT
	960	0.056	+		+	+		80,600	+	+	+	46,230		
(b) (6)	1	<0.025	-		-				-		-			
(B2)	15	<0.025	-		-				-		-			
	388	<0.025	-		-				-		-			
	725	<0.025	+	+	+			47,742	+	+	+	53,220	A/B	WT
(b) (6)	1	<0.025	-		-				-		-			
(B3)	17	9.139	-		-						-			
	24	16.650	-		-						-			
	36	15.340	-		-						-			
	51	6.340	-		-						-			
	80	1.657	-		-						-			
	92	6.078	-		-						-			
	128	2.690	-		-						-			
	142	6.536	-		-				-		-			
	176	3.788	-		-				-		-			
	194	7.674	-		-				-		-			
	393	0.100	+		+			48,500	+	±	+	50,440	AE	WT
	396	0.096	+		+			69,200	+	+	+	93,510		

Subject (Code)[1]	Day[2]	CAB[3] (mcg/mL)	Site Diagnostics: Rapid Tests 1	Rapid Tests 2	Ag/Ab Tests 1	Ag/Ab Tests 2	HIV-1 RNA[4] Qual	HIV-1 RNA[4] (c/mL)	Central: Ag/Ab	Ab	HIV-1 RNA[4] Qual	HIV-1 RNA[4] (c/mL)	ST[5]	INSTI RAS[6]
HPTN 084														
(b) (6)	-12		-	-	-			ND						
	1	<0.025	-	-	-				-		-			
	15	0.057	-	-	-						-			
	29	0.056	-	-	-						-			
	37	0.287	-	-	-						-			
	66	<0.025	-	-	-						-			
	164	<0.025	-	-	-				-		-			
	190	<0.025	-	-	-				-		-			
	275	<0.025	-	-	-				-		-			
	402	<0.025	+	+	+			37,379	+	±	+	42,810	C	WT
	403	<0.025	+	+	+			14,615	+	±	+	32,720		
	535	<0.025						24,750	+	+	+	44,870	C	WT
(b) (6)	-8		-	-	-			ND						
	1	<0.025	-	-	-				-		-			
	15	<0.025	-	-	-				-		-			
	26	<0.025	-	-	-				-		-			
	77	<0.025	+	+	+				+	+	+	26,840	C	WT
	78	<0.025	+	+	+			37,706	+	+	+	31,420		

			Site Diagnostics						Central					
			Rapid Tests		Ag/Ab Tests		HIV-1 RNA[4]		Ag/		HIV-1 RNA[4]			
Subject (Code)[1]	Day[2]	CAB[3] (mcg/mL)	1	2	1	2	Qual	(c/mL)	Ab	Ab	Qual	(c/mL)	ST[5]	INSTI RAS[6]
(b) (6)	-7		-	-	-			ND						
	1	<0.025	-	-	-				-		-			
	15	<0.025	-	-	-						-			
	30	<0.025	-	-	-						-			
	39	<0.025	-	-	-						-			
	46	1.759	-	-	-						-			
	79	4.041	-	-	-						-			
	93	5.897	-	-	-						-			
	109	4.927	-	-	-						-			
	148	2.637	-	-	-				-		-			
	169	1.687	-	-	-				-		-			
	211	2.542	-	-	-				-		-			
	317	1.704	-	-	-				-		-	ND		
	351	2.722	-	-	-				-		-			
	409		-	-	-				-		-			
	522	0.416	-	-	+			1,000,879	+	-	+	875,200	C	WT
	526	1.217	-	-	+			2,709,014	+	-	+	3,927,990	C	WT
	604	0.532							+	±	+	<40		
	710	0.207							+	-	+	<40		
	814	0.039							+	±	-	ND		
	900	<0.025							+	-	+	ND		

Subject (Code)[1]	Day[2]	CAB[3] (mcg/mL)	Site Diagnostics: Rapid Tests 1	Site Diagnostics: Rapid Tests 2	Site Diagnostics: Ag/Ab Tests 1	Site Diagnostics: Ag/Ab Tests 2	Site Diagnostics: HIV-1 RNA[4] Qual	Site Diagnostics: HIV-1 RNA[4] (c/mL)	Central: Ag/Ab	Central: Ab	Central: HIV-1 RNA[4] Qual	Central: HIV-1 RNA[4] (c/mL)	ST[5]	INSTI RAS[6]
(b) (6)	-10		-		-			ND						
	1	<0.025	-		-				-		+	<40		
	15	6.958	-		-				-		+	500	A1	WT
	26	0.147	-		-				-		+	1,740	A1	WT
	33	<0.025	-		-				-		+	6,300	A1	WT
	38	0.557	-		-				+	±	+	87		
	60	0.841	-		-				-		-			
	81	2.336	-		-				-		-			
	114	1.934	-		-				-		-			
	148	3.853	-		-				-		-			
	173	1.754	-		-				-		-			
	227	2.581	-		+			ND	+	±	-			
	247	2.159	-		-			ND	+	±	-			
	275	1.667	-		+			ND	+	±	-			
	325	1.310	-	+	-			ND	+	±	-			
	401	0.701	-	-	-			33	+	±	-			

Source: Supplemental Virology Report (201738 / HPTN 083); Supplemental Virology Report (201739 / HPTN 084); ex.xpt, mb.xpt, pc.xpt, pf.xpt (HPTN 083 supplemental); ex.xpt, mb.xpt, pc.xpt (HPTN 084), pf.xpt (HPTN 084 supplemental); Software: JMP 15; Excel 365

[1] Applicant-assigned code for subjects shown in parenthesis.

[2] Days with CAB injections indicated by bold, italicized text

[3] Plasma CAB concentration. Lower limit of quantification =0.025 µg/mL.

[4] HIV-1 RNA as detected by a qualitative (Qual) or quantitative assay (HIV-1 RNA copies/mL [c/mL]). <LLOQ = HIV-1 RNA detected but below the LOD; <LOD = HIV-1 RNA not detected. LLOQ and LOD =40 copies/mL

[5] HIV-1 subtype

[6] INSTI resistance-associated substitutions

Abbreviations: +, detected; -, not detected; ±, indeterminant; c/mL, HIV-1 RNA copies/mL; CAB, cabotegravir; F/U, Follow-Up Visit; HIV-1, human immunodeficiency virus type 1; INSTI, integrase strand-transfer inhibitor; LLOQ, lower limit of quantification (0.025 mcg/mL for plasma CAB measurements); LOD, limit of detection; Qual, qualitative; RAS, resistance-associated substitution; ST, subtype; WT, wild-type (i.e., absence of major INSTI resistance-associated substitutions)

Infections *in the TDF/FTC Arms of HPTN 083 and HPTN 084*

A summary of the plasma tenofovir (TFV) concentrations, tenofovir diphosphate (TFV-DP) concentrations in DBS, HIV-1 diagnostic data, and virologic data for subjects who became infected while assigned to use TDF/FTC for PrEP in HPTN 083 and HPTN 084 are summarized in Table 134. This summary is limited to those time points spanning from the last negative to the first positive time points, with time points associated with additional genotypic data also shown.

Analysis of ARV concentrations have been used to provide an objective measure of adherence to oral TDF/FTC for PrEP (Castillo-Mancilla et al. 2016; Hendrix et al. 2016; Anderson et al. 2018). In plasma, TFV has a half-life of approximately 15 hours, while intracellular TFV-DP in DBS has a half-life of approximately 17 days. According to Marzinke and colleagues (Marzinke et al. 2021), the plasma TFV assay provides insight into product adherence with a window of 1 to 2 weeks after TDF/FTC cessation. However, interpreting these results should be done carefully because the short half-life of the analyte makes it difficult to distinguish periods of consistent product use from periods of poor adherence with product used immediately before the assessment. In contrast, the TFV-DP concentration data provide insight into product adherence over the preceding 2 to 3 months, where TFV-DP concentrations have been associated with a quantitative estimate of adherence as follows: <350 fmol/punch (<2 doses/week), 350 to <700 fmol/punch (2 to 3 doses/week), 700 to 1,249 fmol/punch (4 to 6 doses/week), and ≥1,250 fmol/punch (7 doses/week).

Three of the 78 infections among the subjects assigned to use TDF/FTC for PrEP were determined retrospectively to have been prevalent infections. Fifty-two percent (39/75) of subjects with incident infections had TFV-DP concentration data at the time of HIV-1 diagnosis. Of these, only 1 subject (HPTN 083 Subject (b) (6) had TFV-DP concentrations consistent with high adherence, at 1,663 fmol/punch.

Viruses from 94% (73/78) of subjects who were, or who became, infected while assigned to use TDF/FTC for PrEP were genotyped successfully. Two of the three subjects with prevalent infections in HPTN 083 developed NRTI RAS-expressing variants from wild-type (i.e., without NRTI RAS) virus at baseline. Subject (b) (6) developed an M184I/V-expressing variant by Day 15, and Subject (b) (6) developed an M184I-expressing variant by Day 35. The third subject with a prevalent infection, Subject (b) (6) maintained wild-type virus through Day 37, the last time point virus was genotyped.

Wild-type viruses were detected in 93% (65/70) of subjects who experienced incident infections, consistent with the overall low level of adherence observed at the times of HIV-1 diagnosis. The remaining 5 subjects had viruses expressing NRTI RAS, including 1 virus expressing K65R, 1 virus expressing M184I, and 3 viruses expressing M184V. The K65R-expressing virus was detected in Subject (b) (6) who was the only subject with TFV-DP levels at the time of HIV-1 diagnosis consistent with a high level of TDF/FTC adherence. It is possible that this apparent breakthrough infection was due to the acquisition of the TFV-resistant virus. It is unclear whether the M184I and M184V-expressing variants were acquired or selected during periods of intermittent TDF/FTC use.

Table 134. Data for HIV-1 Infections Among Subjects Assigned to the TDF/FTC Arms, Trials HPTN 083 and HPTN 084

				Site Diagnostics						Central					
				Rapid Tests		Ag/Ab Tests		HIV-1 RNA[3]				HIV-1 RNA[3]			
Subject	Day	TFV-DP[1] (fmol/punch)	TFV[2] (ng/mL)	1	2	1	2	Qual	(c/mL)	Ag/Ab	Ab	Qual	(c/mL)	ST[4]	NRTI RAS[5]
HPTN 083															
(b) (6)	43		56	-		-				-		-			
	155		56.7	+		+		+	145	+	+	+	51		
	248		<0.31	-		-				-		-			
	387	<31.3	<0.31	+	+	+		+	78,281	+	+	+	52,900	B	WT
	179	74.1	<0.31	-		-						-			
	200		<0.31	-		-				-		+	13,230	B	WT
	234	<31.3	<0.31	+		+			322,900	+	+	+	375,210	B	WT
	315		<0.31	-		-				-		-			
	368	<31.3	<0.31	+		+	+		700,850	+	+	+	543,020	B	WT
	287	46	<0.31	-		-				-		-			
	307		<0.31	-		+	-		10,000,000	+	-	+	36,976,550	BF	M184V
	300		112	-		-				-		-			
	344	115	200	+		+	+		5,175,732	+	+	+	9,751,430	B	WT
	529		<0.31	-		-				-		-			
	579	<31.3	<0.31	+	+	+		+	1,469,874	+	+	+	903,765	F1	WT
	57	77.6	<0.31	-		-				-		+	22,070	B	WT
	429	<31.3	5.93	+	+	+			10,514	+	+	+	4,160	B	WT
	174	32.9	<0.31	-		-						-			
	195		<0.31	-		+			11,112	-		+	11,310	B	WT
	604		<0.31	-		-				-		-			
	617	<31.3	<0.31	-		+		+		+	-	+	505,690	B	WT
	300		<0.31	-		-				-		-			
	337	<31.3	<0.31	+		+		+	130,000	+	+	+	146,260	B	WT
	522		<0.31	-		-						-			
	574	78.2	375	-		-				-		+	20,350	B	WT
	585			-		-				-		+	7,630	B	WT
	806		5.37	-		-				-		-			
	846	106	<0.31	+	+	+		+	10,000,000	+	+	+	53,021,030	B	WT
	697		<0.31	-		-				-		-			
	739		<0.31	-		+			897,000	+	-	+	476,020	B	WT
	240		22.2	-		-				-		-			
	281	111	0.34	+		+	+		16,633	+	+	+	111,820	B	WT

				Site Diagnostics						Central					
				Rapid Tests		Ag/Ab Tests		HIV-1 RNA[3]				HIV-1 RNA[3]			
Subject	Day	TFV-DP[1] (fmol/punch)	TFV[2] (ng/mL)	1	2	1	2	Qual	(c/mL)	Ag/Ab	Ab	Qual	(c/mL)	ST[4]	NRTI RAS[5]
(b) (6)	341	1315	68.5	-		-				-		-			
	351		252	-		-				-		-			
	404	1663	107	+		+	+		2,507	+	+	+	2,720	B	K65R
	71		<0.31	-		-				-		-			
	116	63.5	79	+		+	+		447	+	+	+	2,110	AE	WT
	351	<31.3	<0.31	-		-						-			
	365		<0.31	-		-				-		+	165		
	393	<31.3	<0.31	+		+		+	167,000	+	+	+	228,062	B	WT
	211		29.4	-		-				-		-			
	232	42.6	<0.31	-		-				-		+	<40		
	239			-		-				-		+	26,910	AE	WT
	293	43.2	27.1	+		+				+	+	+	19,260	AE	WT
	124		<0.31	-		-				-		-			
	229	<31.3	<0.31	+		+				+	+	+	7,820	C	WT
	288	34.5	<0.31	-		-				-		-			
	305		<0.31	-		+				+	-	+	19,507,790	C	WT
	686		<0.31	-		-				-		-			
	763	<31.3	<0.31	+		+	+	+	2,093	+	+	+	1,680	B	WT
	89	<31.3	<0.31	-	-	-									
	96		<0.31	-	-	-				-		-			
	137	<31.3	<0.31	-	-	+			221,834	+	-	+	204,580	B	WT
	420	57.3	<0.31	-		-									
	428		10.4	-		-				-		-			
	471	40.8	<0.31	-		+	±	+		+	±	+	9,120	B	M184V
	903	385	46.9	-		-									
	911		0.387	-		-				-		-			
	960	263	21.1	+		+			260,559	+	+	+	211,570	B	M184I
	133		<0.31	-		-				-		-			
	175	<31.3	<0.31	+					10,678	+	+	+	4,510	B	WT
	302		<0.31	-	-	-				-		-			
	365	<31.3	<0.31	-	-	+			>10,000,000	+	±	+	28,637,470	B	WT
	1		<0.31	-		-				-		+	10,000	B	WT
	15		34.7	-		+			127,408	+	-	+	119,990	B	M184I/V
	71		<0.31	-		-				-		-			
	120	109	<0.31	+		+			193,051	+	+	+	882,100	B	WT

Subject	Day	TFV-DP[1] (fmol/punch)	TFV[2] (ng/mL)	Site Diagnostics: Rapid Tests 1	Site Diagnostics: Rapid Tests 2	Site Diagnostics: Ag/Ab Tests 1	Site Diagnostics: Ag/Ab Tests 2	Site Diagnostics: HIV-1 RNA[3] Qual	Site Diagnostics: HIV-1 RNA[3] (c/mL)	Central: Ag/Ab	Central: Ab	Central: HIV-1 RNA[3] Qual	Central: HIV-1 RNA[3] (c/mL)	ST[4]	NRTI RAS[5]
	46		<0.31	-		-				-		-			
(b) (6)	64	52.8	<0.31	-		-				-		+	2,420	B	WT
	71		<0.31	-		+			1,917,663	+	-	+	1,943,850	B	WT
	1		<0.31	-		-				-		+	124		
	15			-		-				-		+	ND		
	30	178	<0.31	-		-				-		+	2,930	B	WT
	37		<0.31	-		+			17,272	+	±	+	13,169	B	WT
	966		<0.31	-		-				-		-			
	1087	<31.3	4.99	+		+			388	+	+	+	490		
	461		<0.31	-		-				-		-			
	510	<31.3	<0.31	+	+	+		+	220,000	+	+	+	154,470	B	WT
	642		<0.31	-		-				-		-			
	679	<31.3	<0.31	-		+		+		+	-	+	1,023,293	B	WT
	36	245	41	-	-	-				-		-			
	260	<31.3	<0.31	+	+	+			588,000	+	+	+	226,400	B	WT
	408		<0.31	-		-				-		-			
	505	<31.3	<0.31	+		+	+		1,040,000	+	+	+	813,790	B	WT
	1		<0.31	-		-				-		+	1,930	B	WT
	18			-		-				-		+	570		
	35	620	73.7	-		+				+	-	+	1,000	B	M184I
	411		<0.31	-		-				-		-			
	468	<31.3	<0.31	+		+	±		341,000	+	±	+	143,510	B	WT
	365		<0.31	-		-				-		-			
	382			-		+			>10,000,000						
	388	140	0.439	+		+			644,808	+	+	+	745,110	AG	WT
	70		2.87	-		-						-			
	119	63.6	<0.31	-		-				-		+	ND		
	134		<0.31	-		+			352,000,000	+	-	+	14,886,030	BC	WT
	307	<31.3	<0.31	-		-				-		-			
	321		<0.31	-		+			1,420,000	+	-	+	2,112,430	AE	WT
	967		<0.31	-		-				-		-			
	1009	<31.3	<0.31	+	+	+		+	40,500	+	+	+	34,180	B	WT

				Site Diagnostics						Central					
				Rapid Tests		Ag/Ab Tests		HIV-1 RNA[3]				HIV-1 RNA[3]			
Subject	Day	TFV-DP[1] (fmol/punch)	TFV[2] (ng/mL)	1	2	1	2	Qual	(c/mL)	Ag/Ab	Ab	Qual	(c/mL)	ST[4]	NRTI RAS[5]
HPTN 084															
	61		112	-	-	-						-			
	91		36.1	-	-	-				-		+	71		
(b) (6)	117			-	-	-				-		+	ND		
	134			-	-	-				-		+	2,220	C	WT
	624		<0.31	-	-	-				-		-			
	680		<0.31	+	+	+				+	+	+	38,440	C	WT
	236	<31.3	<0.31	-	-	-				-		-			
	288		<0.31	+	+	+			113,881	+	+	+	95,250	C	WT
	454		<0.31	-	-	-				-		-			
	525		<0.31	+	+	+			3,126,079	+	+	+	3,471,250	C/K	WT
	1		<0.31	-	-	-				-		-			
	13		95.6	-	-	+				-		-	ND		
	681		8.78	-	-	-				-		-			
	739	139	<0.31	+	+	+			75,840	+	+	+	61,120	C	WT
	232	<31.3	<0.31	-		-				-		-			
	288		188	-		+			9,199	+	+	+	15,800	A1	WT
	168		<0.31	-	-	-						-			
	234	<31.3	<0.31	-	-	-				-		+	601	C	WT
	284		<0.31	+	+	+			94,306	+	+	+	91,490	C	WT
	410	54.4	1.11	-	-	-				-		-			
	456		<0.31	+	+	+			4,122	+	+	+	2,410	C	WT
	34	64.5	75.65	-		-						-			
	42		0.485	-		-				-		+	<40		
	48		<0.31	-		-				-		+	28,220	C	WT
	64		<0.31	+		+			>ULOQ	+	+	+	2,041,230	C	WT
	345		51.5	-		-				-		-			
	413	96.3	<0.31	-		+			183,550	+	-	+	123,790	C	WT
	36		<0.31	-	-	-				-		-			
	45		43.4	-	-	-				-		+	ND		
	64		<0.31	-	-	+				+	-	+	2,521,950	C	WT
	684		<0.31	-	-	-				-		-			
	744	<31.3	<0.31	-	-	+				+	-	+	10,300	C	WT
	119		<0.31	-	-	-				-		-			
	147		<0.31	+	-	+			>ULOQ	+	±	+	8,600,830	A/C	WT

Subject	Day	TFV-DP[1] (fmol/punch)	TFV[2] (ng/mL)	Site Diagnostics: Rapid Tests 1	Site Diagnostics: Rapid Tests 2	Site Diagnostics: Ag/Ab Tests 1	Site Diagnostics: Ag/Ab Tests 2	Site Diagnostics: HIV-1 RNA[3] Qual	Site Diagnostics: HIV-1 RNA[3] (c/mL)	Central: Ag/Ab	Central: Ab	Central: HIV-1 RNA[3] Qual	Central: HIV-1 RNA[3] (c/mL)	ST[4]	NRTI RAS[5]
(b) (6)	543	161	<0.31	-	-	-				-		-			
	623		<0.31	+	+	+			37,379	+	+	+	49,630	C	WT
	569	341	0.411	-	-	-				-		-			
	625		89.9	+	+	+			33,290	+	+	+	26,160	C	WT
	176		<0.31	-	-	-				-		-			
	231	<31.3	<0.31	-	-	+			5,703,189	+	-	+	198,170	C	WT
	151		<0.31	-	-	-				-		-			
	179		<0.31	-	-	+				+	-	+	1,005,760	A1	WT
	295		<0.31	-	-	-				-		-			
	343		<0.31	+	+	+			100,408	+	+	+	68,990	C	WT
	398	<31.3	<0.31	-	-	-				-		-			
	468		<0.31	+	+	+			2,445,082	+	+	+	3,223,880	C	WT
	491		121	-	-	-				-		-			
	568	36.1	226	+	+	+			52,461	+	+	+	40,570	C	WT
	295		<0.31	-	-	-				-		-			
	344		<0.31	+	+	+				+	+	+	2,706,990	C	WT
	162		<0.31	-	-	-				-		-			
	229	<31.3	<0.31	-	-	-				-		+	2,930	C	WT
	286		<0.31	+	+	+				+	+	+	11,860	C	WT
	182		<0.31	-	-	-				-		-			
	267		<0.31	+	+	+			26,040	+	+	+	28,990	C	WT
	148		<0.31	-		-				-	-	-			
	176		<0.31	-		+				+	-	+	16,844,070	C	WT
	673		43.9	-		-				-		-	ND		
	735	97.4	105.5	+		+			160,387	+	+	+	156,260	C	WT
	807		<0.31	-		-				-		-			
	847		<0.31	+		+				+	+	+	3,010		
	569	151	52.9	-		-				-		-			
	624		45.6	+		+				+	±	+	21,570	C	WT
	631	175		+		+			116,000	+	+	+	13,730	C	WT
	174		<0.31	-	-	-				-		-			
	233	<31.3	<0.31	-	-	+			755,371	+	-	+	720,210	C	WT
	301		14.3	-	-	-				-		-			
	352		<0.31	+	+	+			85,108	+	+	+	64,940	C	WT

Subject	Day	TFV-DP[1] (fmol/punch)	TFV[2] (ng/mL)	Site Diagnostics: Rapid Tests 1	Site Diagnostics: Rapid Tests 2	Site Diagnostics: Ag/Ab Tests 1	Site Diagnostics: Ag/Ab Tests 2	Site Diagnostics: HIV-1 RNA[3] Qual	Site Diagnostics: HIV-1 RNA[3] (c/mL)	Central: Ag/Ab	Central: Ab	Central: HIV-1 RNA[3] Qual	Central: HIV-1 RNA[3] (c/mL)	ST[4]	NRTI RAS[5]
(b) (6)	398	212	68.2	-	-	-				-		-			
	468		55.3	+	+	+			14,043	+	+	+	22,610	C	WT
	41		<0.31	-	-	-				-		-			
	56		<0.31	-	-	-				+	-	+	25,340	C	WT
	95		<0.31	+	+	+			89,239	+	+	+	35,460	C	WT
	400	190	88.4	-	-	-				-		-			
	460		55	-	-	+			9,708,132	+	-	+	8,612,430	C	WT
	296		<0.31	-	-	-				-		-			
	344		<0.31	-	-	+			493,568	+	-	+	757,960	C	WT
	67		<0.31	-	-	-				-		-			
	91		<0.31	-	-	-				-		+	ND		
	124		<0.31	-	-	+			677,990	+	-	+	655,530	C	M184V
	82		76	-	-	-						-			
	117		108	-	-	-				-		+	ND		
	152		109	+	+	+			527	+	+	+	1,600		

Source: Supplemental Virology Report (201738 / HPTN 083); Supplemental Virology Report (201739 / HPTN 084); ex.xpt, mb.xpt, pc.xpt, pf.xpt (HPTN 083 supplemental); ex.xpt, mb.xpt, pc.xpt (HPTN 084), pf.xpt (HPTN 084 supplemental); Software: JMP 15; Excel 365

[1] Lower limit of quantification =31.3 fmol/punch

[2] Lower limit of quantification =0.31 ng/mL

[3] HIV-1 RNA as detected by a qualitative (Qual) or quantitative assay (HIV-1 RNA copies/mL [c/mL]). <40 c/mL = HIV-1 RNA detected but below the assay's lower limit of quantification; ND = HIV-1 RNA not detected.

[4] HIV-1 subtype

[5] NRTI resistance-associated substitutions

Abbreviations: +, detected; -, not detected; ±, indeterminant; c/mL, HIV-1 RNA copies/mL; HIV-1, human immunodeficiency virus type 1; ND, not detected; NRTI, HIV-1 nucleos(t)ide reverse transcriptase inh bitor; Qual, qualitative; RAS, resistance-associated substitution; ST, subtype; ULOQ, upper limit of quantification; WT, wild-type (i.e., absence of major NRTI resistance-associated substitutions)

19. Other Drug Development Considerations: Additional Information and Assessment

Not applicable

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

Not applicable

21. Labeling Summary of Considerations and Key Additional Information

The Applicant's proposed labels for APRETUDE and VOCABRIA, submitted on July 23, 2021, were compared with the final agreed upon labeling for both applications. This review summarizes the major label changes. Most of the changes outlined below apply to both APRETUDE and VOCABRIA. However, the two labels have different levels of detail and different subsection numbers. For this reason, if the change only applies to one label it is noted in the review below.

1 INDICATIONS AND USAGE

Indications were modified to add "adolescents" based on interim data from ongoing trials in adolescent males and females.

2 DOSAGE AND ADMINISTRATION

2.2 HIV-1 Screening for Individual Receiving APRETUDE for HIV-1 PrEP [subsection 2.2 for VOCABRIA - HIV-1 Screening for Individuals for HIV-1 PrEP]

This subsection in both labels was updated to provide additional details to ensure testing was done prior to each injection (or oral cabotegravir) and specifies recommendations for testing methods as follows:

Individuals must be tested for HIV-1 infection prior to initiating APRETUDE or oral cabotegravir, and with each subsequent injection of APRETUDE, using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. If an antigen/antibody-specific test is used and provides negative results, then such negative results should be confirmed using an RNA-specific assay, even if the results of the RNA-assay are available after APRETUDE or oral cabotegravir administration.

2.4 Optional Oral Lead-in Dosing to Assess Tolerability of APRETUDE

This subsection was updated to provide the rationale for the optional oral lead-in, specifically, no safety and efficacy data are available for use of APRETUDE without an oral lead-in *[see Warnings and Precautions (5.3), Adverse Reactions (6.1)]*. However, in HIV-1 treatment clinical trials, data show that an oral lead-in is not needed to ensure adequate plasma cabotegravir exposure upon initiation of injections and that the safety and efficacy results of CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension) were similar when administered with and without an oral lead-in.

2.5 Gluteal Intramuscular Injection Dosing with APRETUDE

This subsection was reformatted to provide clear instructions for initiation and continuation injections, along with recommended dosing schedule with an oral lead-in or direct to injection.

5 WARNINGS AND PRECAUTIONS

5.1 Comprehensive Management to Reduce the Risk of HIV-1 Infection

This subsection in both labels were revised for consistency with the Descovy label and to emphasize testing requirements prior to each injection (or use of oral cabotegravir).

5.6 Depressive Disorder

This subsection in both labels was added because cases were reported with CAB in other clinical trials. The phase 2 data for oral CAB showed depressive disorders were related to CAB in the absence of RPV. The following text was added.

Depressive disorders (including depression, depressed mood, major depression, persistent depressive disorder, suicide ideation or attempt) have been reported with APRETUDE [see Adverse Reactions (6.1)]. Promptly evaluate individuals with depressive symptoms to assess whether the symptoms are related to APRETUDE and to determine whether the risks of continued therapy outweigh the benefits.

In the VOCABRIA label, the statement above was added under the When VOCABRIA is Used for HIV-1 PrEP subsection.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience (APRETUDE)

This subsection was updated as follows:

- To provide more details regarding injection site reactions and focused on those reactions seen among participants who received APRETUDE and experienced at least on injection site reaction.
- To update the (b) (4) vomiting, myalgia and rash. These events are included in the main adverse reaction table because the events were seen in at least 1% of participants in either HPTN 083 or HPTN 084.

- Include in the laboratory abnormalities section a table for Grade 3 and 4 abnormalities that occurred in ≥ 1% of participants in either HPTN 083 or HPTN 084 and a table for fasting lipid values, median change from baseline at Week 57 reported in HPTN 083 and HPTN 084.
- Include a Clinical Trial Experience in Adolescents section to state, in adolescents receiving APRETUDE for HIV-1 PrEP, the safety data were comparable to the safety data reported in adults receiving APRETUDE for HIV-1 PrEP. Similar updates were made to the VOCABRIA label.

In the VOCABRIA labels (b) (4) were removed (b) (4).

8.4 Pediatric Use

This subsection was added in both labels to provide the basis for the indication and dosing in adolescents as follows:

The safety and effectiveness of APRETUDE for HIV-1 PrEP in at-risk adolescents weighing at least 35 kg is supported by data from 2 adequate and well-controlled trials of APRETUDE for HIV-1 PrEP in adults with additional safety and pharmacokinetic data from studies in HIV-1 infected adults who were administered CABENUVA, and in HIV-1 infected pediatric subjects who were administered separate components of CABENUVA in addition to their current antiretroviral therapy *[see Dosage and Administration (2.5), Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.2)]*.

APRETUDE for HIV-1 PrEP is being evaluated in 2 open-label multicenter clinical trials in adolescent individuals. Fifty-nine adolescents have been enrolled. Of these, 54 adolescent participants received one or more injections. In adolescents receiving APRETUDE for HIV-1 PrEP, the safety data were comparable to the safety data reported in adults receiving APRETUDE for HIV-1 PrEP.

While using APRETUDE, HIV-1 testing should be conducted prior to initiating APRETUDE (with or without an oral lead-in with oral cabotegravir) and prior to each injection of APRETUDE. Adolescents may benefit from more frequent visits and counseling to support adherence to the dosing and testing schedule *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*.

The safety, efficacy, and pharmacokinetics of APRETUDE in pediatric participants younger than 12 years of age or weighing <35 kg have not been established.

12.4 Microbiology

More details in both labels regarding the incident and prevalent infections were included along with updated information on cross-resistance.

14 CLINICAL STUDIES

14.1 Clinical Trials in Adults for HIV-1 Pre-Exposure Prophylaxis (APRETUDE)

This subsection was updated to include the efficacy results from the extended retrospective virologic testing with readjudicated endpoints for both trials after the primary efficacy analyses.

One of the 13 HIV-1 incident infections in the APRETUDE arm in HPTN 083 was determined to be a prevalent infection. One of the 4 HIV-1 incident infections in the APRETUDE arm in HPTN 084 was determined to be a prevalent infection. The hazard ratio (95% CI) and p-values were updated accordingly for both trials. Additionally, the incident HIV-1 infections by subgroup tables were updated.

In the VOCABRIA label, this subsection was streamlined to reference the trial descriptions for HPTN 083 and HPTN 084 and to refer to the APRETUDE prescribing information for additional details.

17 PATIENT COUNSELING INFORMATION

Both labels were updated for consistency with the full prescribing information.

22. Postmarketing Requirements and Commitments

The following studies will be conducted as postmarketing requirements (PMR).

APRETUDE

4191-1 Conduct a trial to evaluate the safety, tolerability, and acceptability of cabotegravir extended-release injectable suspension (CAB LA) for pre-exposure prophylaxis (PrEP) in adolescents weighing at least 35 kg, who are at risk of sexually acquired HIV-1 infection. The trial should capture data on resistance among participants who become infected during PrEP use or within one year of discontinuing PrEP.

a) Adherence data

b) Information on adverse events and treatment discontinuations

c) Information on patterns of sexual risk behavior over time

d) Resistance analyses of viral isolates from those who acquire HIV-1, including a description of the methodologies used to evaluate resistance

e) Pharmacokinetic data

Submit Clinical Study Reports (CSR) from the HPTN adolescent sub-studies and from the MOCHA study.

Study Completion: 05/2023

Final Report Submission: 06/2024

4191-2 Conduct a study to collect and analyze data from adults and adolescents who take cabotegravir extended-release injectable suspension (CAB LA) for pre-exposure prophylaxis (PrEP) of sexually acquired HIV-1 infection and who become infected during PrEP use or within one year of discontinuing PrEP. As part of this study, collect and provide information on

adherence, risk factors for non-adherence and HIV-1 acquisition. To compare tolerability and rates of HIV-1 acquisition among patients who initiate CAB LA with an oral lead-in to those who directly initiate CAB LA injections, the following should be included in the study report:

a) Frequency of testing and methods used for HIV-1 diagnosis.

b) Frequency of prevalent HIV-1 infections that were detected, including those captured during screening.

c) Resistance analyses of viral isolates from those who acquire HIV-1, including a description of the methodologies used to evaluate resistance.

d) Description of subsequent antiretroviral therapy, including the time required to achieve virologic suppression and the durability of the response (to cover 48-weeks from the time therapy is initiated, at minimum).

e) Information on adherence, select adverse events and treatment discontinuations.

Final Protocol Submission: 03/2022

Study Completion: 04/2027

Final Report Submission: 03/2028

VOCABRIA

4196-1 Conduct a study to collect and analyze data from adults and adolescents who take cabotegravir extended-release injectable suspension (CAB LA) for pre-exposure prophylaxis (PrEP) of sexually acquired HIV-1 infection and who become infected during PrEP use or within one year of discontinuing PrEP. As part of this study, collect and provide information on adherence, risk factors for non-adherence and HIV-1 acquisition. To compare tolerability and rates of HIV-1 acquisition among patients who initiate CAB LA with an oral lead-in to those who directly initiate CAB LA injections, the following should be included in the study report:

a) Frequency of testing and methods used for HIV-1 diagnosis.

b) Frequency of prevalent HIV-1 infections that were detected, including those captured during screening.

c) Resistance analyses of viral isolates from those who acquire HIV-1, including a description of the methodologies used to evaluate resistance.

d) Description of subsequent antiretroviral therapy, including the time required to achieve virologic suppression and the durability of the response (to cover 48-weeks from the time therapy is initiated, at minimum).

e) Information on adherence, select adverse events and treatment discontinuations.

Final Protocol Submission: 03/2022

Study Completion: 04/2027

Final Report Submission: 03/2028

23. Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators* (February 2013) and by 21 CFR 54.4.

Table 135. Covered Clinical Studies: HPTN 083, HPTN 084, HPTN 077, and ECLAIR

Was a list of clinical investigators provided:	Yes ☐ ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1736 (including principal investigators and sub investigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 27 (some investigators were counted more than once if involved in more than one study or at more than one site)		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 26 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 1 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 197		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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25. Review Team

Table 136. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	London Harrison, MBEE
Nonclinical Reviewer	David McMillan, PhD, DABT Ilona Bebenek, PhD, DABT
Nonclinical Team Leader	Peyton Myers, PhD, DABT
Virology Reviewer(s)	Damon Deming, PhD Lisa Naeger, PhD
Virology Team Leader	Julian O'Rear, PhD
Office of Clinical Pharmacology Reviewer(s)	Mario Sampson, PharmD
Office of Clinical Pharmacology Team Leader(s)	Justin C. Earp, PhD Vikram Arya, PhD, FCP
Clinical Reviewer	Aimee Hodowanec, MD
Clinical Team Leader	Kimberly Struble, PharmD
Statistical Reviewer	Wen Zeng, PhD
Statistical Team Leader	Thamban Valappil, PhD
Cross-Disciplinary Team Leader	Kimberly Struble, PharmD
Division Director (pharm/tox)	Hanan Ghantous, PhD, DABT
Division Director (OB)	Dionne Price, PhD
Division Director (clinical)	Debra Birnkrant, MD
Deputy Director (acting)	Yodit Belew, MD
Deputy Director of Safety	Poonam Mishra, MD, MPH

Abbreviations: OB , Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 137. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	
CMC ATL	Peter Guerrieri, PhD
Drug Product	Peter Guerrieri, PhD
Drug Substance	Kabir Shahjahan, PhD (Primary) / Paresma Patel, PhD (Secondary)
Biopharmaceutics	Gerlie Gieser PhD, (Primary) / Elsbeth Chikhale, PhD (Secondary)
Process	Jin Lee, PhD (Primary) / Yiwei Li, PhD (Secondary)
RBPM	Shamika Brooks, PharmD
Microbiology	Sallie Crenshaw, PhD (Primary / Erika Pfeiler, PhD (Secondary)
OPDP	Wendy Lubarsky, PharmD Sam Skariah, PharmD, RAC
DMPP	Shawna Hutchins, MPH, BSN, RN Barbara Fuller, RN, MSN, CWOCN
OSI	Jenn Sellers, MD, PhD Philip Kronstein, MD
OSE/DEPI	Hannah Day, PhD Natasha Pratt, PhD
OSE/DMEPA	Melina Fanari, R. Ph (Primary) Sevan Kolejian, PharmD, MBA, BCPPS (TL)
OSE/DRISK	Joyce Weaver, PharmD
Clinical Data Scientist	Anne Bunner, PhD DeAngelo McKinley, PharmD, PhD (TL)
Medical Editors	Hyo Sook Song (Primary) Pamela Hsieh

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Table 138. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Debra Birnkrant, MD	OND/OID/DAV	☐ Authored ☒ Approved
Division Director	**Signature:**		
Clinical	Yodit Belew, MD	OND/OID/DAV	☐ Authored ☐ Contributed ☒ Approved
Deputy Director (Acting)	**Signature:** Yodit Belew -S Digital y s gned by Yodit Belew S DN c=US o=U S Government ou=HHS ou=FDA ou=People cn=Yodit Be ew S 0 9 2342 19200300 100 1 1=1302232409 Date 2021 12 20 11 47 08 05'00'		
Clinical	London Harrison	OND/ORO/DROID	☒ Authored 12 ☐ Contributed ☐ Approved
Project Manager	**Signature:** London Harrison -S Digitally signed by London Harrison -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011543164, cn=London Harrison -S Date: 2021.12.17 13:37:20 -05'00'		
Clinical	Aimee Hodowanec, MD	OND/OID/DAV	☒ Authored 1-4, 7, 10, 11, 17, 22, 23 ☒ Contributed 6, 8, 15 ☒ Approved
Primary Reviewer	**Signature:** Aimee Hodowanec -S Digitally signed by Aimee Hodowanec S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=2001901416 cn=Aimee Hodowanec S Date: 2021 12 20 11:15:34 05'00'		
Clinical	Kimberly Struble, PharmD	OND/OID/DAV	☒ Authored 1-4, 6, 7, 8, 10, 11, 15, 17, 21, 22, 23 ☐ Contributed ☒ Approved
Cross-Disciplinary Team Lead	**Signature:** Kimberly A. Struble -S Digitally signed by Kimberly A. Struble -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300077275, cn=Kimberly A. Struble -S Date: 2021.12.20 11:36:26 -05'00'		
Clinical Virology	Damon Deming, PhD	OND/OID/DAV	☒ Authored 7, 18 ☒ Contributed 5.1 ☒ Approved
Reviewer	**Signature:**		
Clinical Virology	Lisa Naeger, PhD	OND/OID/DAV	☐ Authored ☐ Contributed ☒ Approved 7, 18
Reviewer	**Signature:** Lisa K. Naeger -S Digitally signed by Lisa K. Naeger -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lisa K. Naeger -S, 0.9.2342.19200300.100.1.1=1300191458 Date: 2021.12.17 16:32:29 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Virology	Julian O'Rear, PhD	OND/OID/DAV	☐ Authored ☒ Contributed 5.1 ☒ Approved 7, 18
Team Leader	**Signature:** Julian J. O'rear -S Digitally signed by Julian J. O'rear -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300150659, cn=Julian J. O'rear -S Date: 2021.12.20 10:02:59 -05'00'		
Clinical Pharmacology	Mario Sampson, PharmD	OTS/OCP/DIDP	☒ Authored 5, 6.1.1, 7, 8.1, 8.2, 14 ☒ Contributed 7.7.1, 7.7.2, 8.3 ☐ Approved
Reviewer	**Signature:** Mario Sampson -S Digitally signed by Mario Sampson S DN: c=US o=U S Government ou=HHS ou=FDA ou=Peop e cn=Mario Sampson S 0 9 2342 19200300 100 1 1=2001365806 Date: 2021 12 17 15:38:48 06 00		
Clinical Pharmacology	Vikram Arya, PhD, FCP	OTS/OCP/DIDP	☒ Authored ☒ Contributed ☒ Approved 5, 6.1.1, 7.7.1, 7.7.2, 8.1, 8.2, 8.3, 14
Team Leader	**Signature:** Vikram Arya -S Digitally signed by Vikram Arya -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Vikram Arya -S, 0.9.2342.19200300.100.1.1=1300221914 Date: 2021.12.18 12:53:18 -05'00'		
Clinical Pharmacology/Pharmacometrics	Justin C. Earp, PhD	OTS/OCP/DPM	☐ Authored ☐ Contributed ☒ Approved 14
Team Leader	**Signature:** Justin C. Earp -S Digitally signed by Justin C. Earp -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Justin C. Earp -S, 0.9.2342.19200300.100.1.1=1300436664 Date: 2021.12.20 11:27:34 -05'00'		
Biometrics	Wen Zeng, PhD	OTS/OB/DBIV	☒ Authored 6.2.1.1, 6.2.1.3, 6.2.1.4, 6.2.2.1, 6.2.2.3, 6.2.2.4, 16 ☒ Contributed 6.2, 6.3 ☒ Approved
Reviewer	**Signature:** Wen Zeng -S Digitally signed by Wen Zeng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Wen Zeng -S, 0.9.2342.19200300.100.1.1=2000584499 Date: 2021.12.20 08:09:15 -05'00'		
Biometrics	Thamban Valappil, PhD	OTS/OB/DBIV	☐ Authored ☐ Contributed ☒ Approved 6.2.1.1, 6.2.1.3, 6.2.1.4, 6.2.2.1, 6.2.2.3, 6.2.2.4, 6.3, 16
Team Leader	**Signature:** Thamban I. Valappil -S Digitally signed by Thamban I. Valappil -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300151694, cn=Thamban I. Valappil -S Date: 2021.12.17 20:25:21 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Biometrics	Dionne Price, PhD	OTS/OB/DBIV	☐ Authored ☐ Contributed ☒ Approved 6.2.1.1, 6.2.1.3, 6.2.1.4, 6.2.2.1, 6.2.2.3, 6.2.2.4, 6.3, 16
Division Director	**Signature:** Dionne L. Price -S Digitally signed by Dionne L. Price -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300164533, cn=Dionne L. Price -S Date: 2021.12.20 09:46:01 -05'00'		
Cross-Disciplinary	Stacey Min, PharmD	OND/OID/DAV	☒ Authored 21 ☐ Contributed ☒ Approved
Associate Director for Labeling	**Signature:**		
Pharmacology/Toxicology	David McMillan, PhD, DABT	OND/OID/DPTID	☐ Authored ☐ Contributed ☒ Approved 7.1, 8.3, 13
Reviewer	**Signature:** David Mcmillan -S Digitally signed by David Mcmillan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=David Mcmillan -S, 0.9.2342.19200300.100.1.1=2001893997 Date: 2021.12.17 15:07:07 -05'00'		
Pharmacology/Toxicology	Ilona Bebenek, PhD, DABT	OND/OID/DPTID	☐ Authored ☐ Contributed ☒ Approved 7.1, 8.3, 13
Reviewer	**Signature:** Ilona Bebenek -S Digitally signed by Ilona Bebenek -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ilona Bebenek -S, 0.9.2342.19200300.100.1.1=2001245411 Date: 2021.12.17 14:08:45 -05'00'		
Pharmacology/Toxicology	Laine Peyton Meyers, PhD, DABT	OND/OID/DPTID	☐ Authored ☐ Contributed ☒ Approved 7.1, 8.3, 13
Team Leader	**Signature:** Laine P. Myers -S Digitally signed by Laine P. Myers -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Laine P. Myers -S, 0.9.2342.19200300.100.1.1=1300389063 Date: 2021.12.17 14:59:17 -05'00'		
Pharmacology/Toxicology	Hanan Ghantous, PhD, DABT	OND/OID/DPTID	☐ Authored ☐ Contributed ☒ Approved 7, 8.3, 13
Division Director	**Signature:** Hanan N. Ghantous -S Digitally signed by Hanan N Ghantous S DN: c US o U S Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 1300169484 cn Hanan N Ghantous S Date: 2021 12 17 15:20:35 05'00'		

Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Cross-Disciplinary	Stacey Min, PharmD	OND/OID/DAV	Enter sections. ☐ Authored ☒ Contributed 21 ☒ Approved 21
Associate Director for Labeling	**Signature:** Stacey Min -S Digitally signed by Stacey Min -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stacey Min -S, 0.9.2342.19200300.100.1.1=2000365089 Date: 2021.12.20 11:48:50 -05'00'		

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LONDON F HARRISON
12/20/2021 12:56:23 PM

DEBRA B BIRNKRANT
12/20/2021 12:57:57 PM