STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3b, Multicenter, Open-Label Study to Evaluate Switching From a Regimen of Two Nucleos(t)ide Transcriptase Reverse Inhibitors (NRTI) plus a Third Agent to a Fixed Dose Combination (FDC) of Bictegravir/ Emtricitabine/Tenofovir Alafenamide (B/F/TAF) in Virologically-Suppressed, HIV-1 Infected African American Participants
Name of Test Drug:	Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF; GS-9883/F/TAF)
Study Number:	GS-US-380-4580
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Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
BIC	bictegravir
B/F/TAF	fixed dose combination of bictegravir (BIC; B) 50 mg / emtricitabine (FTC; F) 200 mg / tenofovir alafenamide (TAF) 25 mg
BMI	body mass index
CDER	Center for Drug Evaluation and Research
CG	Cockcroft-Gault
CI	confidence interval
CRF	case report form
DNA	deoxyribonucleic acid
DTG	dolutegravir
ECG	electrocardiogram
EFV	efavirenz
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate using Cockcroft-Gault formula
FAS	full analysis set
FDA	Food and Drug Administration
FDC	fixed dose combination
GFR	glomerular filtration rate
Gilead	Gilead Sciences, Inc.
GLPS	global patient safety
GS-9883	bictegravir
HBcAb	hepatitis B core antibody
HBeAb	hepatitis B e-antibody
HBeAg	hepatitis B e-antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HDL	high density lipoprotein
HIV-1	human immunodeficiency virus (Type 1)
HLGT	high level group term
HLT	high level term

ID	identification
INSTI	integrase strand-transfer inhibitor
IWRS	interactive web response system
LDL	low density lipoprotein
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
NRTI	nucleos(t)ide reverse transcriptase inhibitors
PP	per protocol
PT	preferred term
Q	quartile
Q1	first quartile
Q3	third quartile
RNA	ribonucleic acid
RPV	rilpivirine
RT	reverse transcriptase
RTV	ritonavir
SAE	serious adverse event
SAP	statistical analysis plan
SBR	stay on baseline regimen
SD	standard deviation
SMQ	Standardised MedDRA Query
SOC	system organ class
TAF	tenofovir alafenamide
TAM	thymidine analogue mutation
TDF	tenofovir disoproxil fumarate
TFL	tables, figures, and listings
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) of the final analysis for Study GS-US-380-4580, which will be performed when all participants have completed the study or prematurely discontinued from the study. This SAP is based on the study protocol dated 27 June 2018 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the clinical study report.

The analyses of the primary and secondary efficacy endpoints were described in the Week 48 SAP. CCI [redacted]

1.1. Study Objectives

The primary objective of this study is:

- To evaluate the efficacy of switching from a regimen of 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and a third agent to a fixed dose combination (FDC) of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) versus continuing their baseline regimen in HIV-1 infected, virologically suppressed African American participants as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24.

The secondary objectives of this study are:

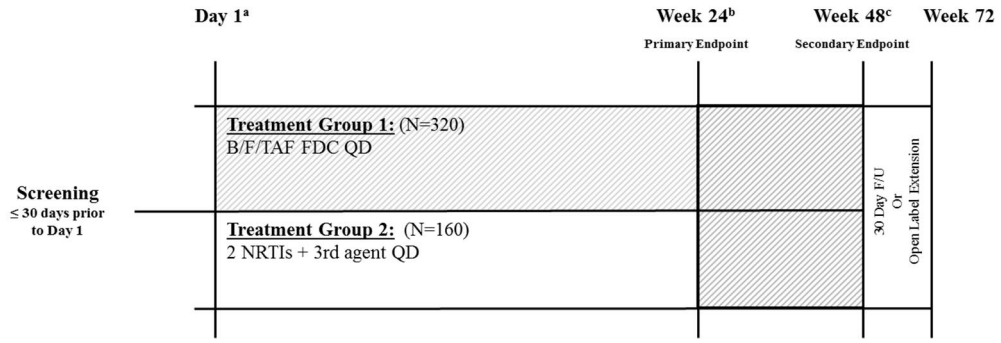
- To evaluate the efficacy of switching to a FDC of B/F/TAF from a regimen of 2 NRTIs and a third agent as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48

- To evaluate the efficacy, safety, and tolerability of switching to a FDC of B/F/TAF from a regimen of 2 NRTIs and a third agent in HIV-1 infected, virologically suppressed African American participants through Week 48

1.2. Study Design

The study schema is provided in Figure 1-1.

Figure 1-1. Study Schema



a Following the Day 1 visit, participants will be required to return for study visits at Weeks 4 and 12, and then every 12 weeks through the Week 48 visit. The Primary Endpoint will be assessed when the last enrolled participant completes the Week 24 visit.

b At Week 24, participants randomized to continue on their baseline regimen who complete 24 weeks of treatment on their baseline regimen will switch to B/F/TAF FDC.

c At Week 48, participants who wish to continue on B/F/TAF will be given the option to receive B/F/TAF FDC for up to an additional 24 weeks or until they have access to B/F/TAF, whichever occurs first, and attend study visits every 12 weeks followed by a 30 Day Follow up Visit.

Design Configuration and Subject Population

GS-US-380-4580 is a randomized, open-label, multicenter, active-controlled study of HIV-1 infected, virologically suppressed African American participants.

Treatment Groups

Participants who provide written consent and meet all eligibility criteria will be randomized in a 2:1 ratio to one of the following 2 treatment groups:

- **Treatment Group 1:** FDC of B/F/TAF (50 mg/ 200 mg/ 25 mg) administered orally, once daily, without regard to food (n 320 planned)

- **Treatment Group 2:** Stay on baseline regimen (SBR) consisting of 2 NRTIs and a third agent (each taken as prescribed) from Day 1 until Week 24, with a delayed switch to a FDC of B/F/TAF (50 mg/ 200 mg/ 25 mg) administered orally, once daily, without regard to food (n 160 planned)

Key Eligibility Criteria

Medically stable HIV-infected participants who meet the following criteria:

- Self-describes as Black, African American, or mixed race, including Black

- Currently receiving an antiretroviral (ARV) regimen other than FDC of B/F/TAF that consists of any two NRTIs + allowed third agent for ≥ 6 months (see Protocol Section 4.2 for allowed agents)

- Have no documented or suspected resistance to integrase strand transfer inhibitors (INSTIs) and no history of virologic failure on an INSTI containing regimen (2 consecutive HIV-1 RNA ≥ 50 copies/mL after achieving < 50 copies/mL while on an INSTI-containing regimen)

- History of 1-2 thymidine analogue mutations (TAMs), M184V/I, and any other reverse transcriptase (RT) substitutions are allowed, with the following exceptions: History of 3 or more TAMs (M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/N/R), T69-insertions, or K65R/E/N in RT will be excluded.

- Documented plasma HIV-1 RNA < 50 copies/mL during treatment with the baseline regimen for a minimum period of 6 months, and at least the last two HIV-1 RNA measurements prior to the Screening visit

- HIV-1 RNA levels < 50 copies/mL at Screening Visit

- Estimated glomerular filtration rate (eGFR) ≥ 50 mL/min according to the Cockcroft-Gault formula for creatinine clearance

- Eligible participants with chronic hepatitis C virus (HCV) infection are permitted to enroll. In addition, eligible participants with chronic hepatitis B virus (HBV) infection are permitted to enroll if their baseline regimen contains either TAF or TDF.

Study Phases

Participants will be treated for at least 48 weeks after randomization (Randomization Phase).

Following the Screening and Day 1 visits, participants will be required to return for study visits at Weeks 4, 12, 24, 36, and 48. Participants randomized to SBR will have, after their delayed switch at Week 24, an additional visit at Week 28.

Participants who complete the study through the Week 48 visit and wish to continue on B/F/TAF, will be given the option to receive FDC of B/F/TAF for up to an additional 24 weeks or until they have access to FDC of B/F/TAF, whichever occurs first, and will attend study visits every 12 weeks followed by a 30-Day Follow-Up Visit. This is the Extension Phase.

Participants who complete the study through the Week 48 Visit and do not continue their participation in the study will be required to return to the clinic 30 days after their Week 48 Visit for a 30-Day Follow-Up Visit.

Schedule of Assessments

After screening procedures, eligible participants will be randomized 2:1 to Treatment Group 1 or Treatment Group 2 and treated for at least 48 weeks. Following the Day 1 visit, participants will return for study visits at Weeks 4, 8, 12, 24, 36 and 48. Participants randomized to SBR will have, after their delayed switch at Week 24, an additional visit at Week 28.

Laboratory analyses (chemistry, hematology, and urinalysis), HIV-1 RNA, CD4+ cell count, assessment of adverse events (AEs) and concomitant medications, and complete or symptom directed physical examinations will be performed at Screening, Day 1 and subsequent study visits. Whole blood for HIV-1 deoxyribonucleic acid (DNA) archive testing will be collected at Day 1 for all participants and at Week 24 for all participants in Treatment Group 2.

Historical HIV-1 RNA genotypes (from resistance testing) will be collected, if available.

More details for study procedures can be found in Appendix 1.

Randomization

Participants will be randomized in a 2:1 allocation ratio to 1 of 2 treatment groups: Treatment Group 1 (B/F/TAF); Treatment Group 2 (SBR)]. Randomization will be stratified by the baseline 3rd agent ARV class at entry (integrase strand transfer inhibitor (INSTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI) or CCR5 antagonist).

Site and/or Stratum Enrollment Limits

Approximately 84 study sites in the United States participated. In order to provide all sites the opportunity to enroll participants, the initial enrollment limit for individual sites was initially set to 6 participants. Additional enrollment slots at an individual site were allocated on a case-by-case basis.

Study Duration

Study duration for each participant will be at least 48 weeks.

1.3. Sample Size and Power

A total of 480 HIV-1 infected participants, randomized in a 2:1 ratio to 2 treatment groups, achieves approximately 89% power to detect a noninferiority margin difference between the group proportions of 6% for HIV-1 RNA ≥ 50 copies/mL at Week 24.

For sample size and power computation, it is assumed that the reference group proportion is 4%. The treatment group proportion is assumed to be 10% under the hypothesis of inferiority. The power is computed for the case when the actual treatment group difference is zero (treatment reference). The test statistic used is the one-sided Score test (Farrington & Manning) with the significance level of 0.025. Sample size and power calculations were performed using the statistical software package PASS (Version 14).

In general, a failure rate of 1% to 3% is assumed for switch studies in virologically suppressed participants, and the noninferiority margin for treatment difference is typically set at 4%. The failure rate of 4% and noninferiority margin of 6% used for this study was based on the observation that African Americans have lower rates of virological suppression compared to other cohorts {DeJesus 2019}. In the United States (US), not all communities have had equitable access to advancements in HIV treatment. African Americans remain disproportionately affected by HIV but have less access to HIV treatment and generally worse health outcomes compared to other racial groups.

Table 1-1 provides approximate power for SBR proportions ranging from 2% to 4% with noninferiority margin ranging from 4% to 6%. A total of 480 HIV-1 infected participants, randomized in a 2:1 ratio to 2 treatment groups, achieves approximately 87% power to detect a noninferiority margin difference between the group proportions of 4%.

Table 1-1. Power for Various Proportions and Noninferiority Margins

SBR Proportion	Noninferiority Margin	Approximate Power	Actual Alpha
4%	6%	91%	0.026
3%	5%	88%	0.026
2%	4%	87%	0.024

SBR N 160; B/F/TAF N 320; alpha targeted at 0.025. The test statistic used is the one sided Score test (Farrington &Manning). Power and actual alpha were computed using binomial enumeration of all possible outcomes.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. Week 24 Analysis

The Week 24 (primary endpoint) analysis was conducted after all participants either completed their Week 24 visit or prematurely discontinued from the study prior to Week 24 and was repeated for the Week 48 analysis.

2.1.2. Week 48 Analysis

The Week 48 analysis was conducted after all participants either completed their Week 48 visit or prematurely discontinued from the study.

2.2. Final Analysis

The final statistical analysis will be conducted after all participants either complete the study or prematurely discontinue from the study.

This SAP describes the analysis plan for the final analysis. This final analysis will include all data from the participants randomized to FDC of B/F/TAF and post Week 24 (delayed switch) data for participants randomized to SBR. Data for the first 24 weeks for the SBR group were presented in the Week 24 and Week 48 analyses and will not be summarized in the final analysis. However, all data (other than patient-reported outcomes) will be included in the listings.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all participants in the All Randomized Analysis Set unless otherwise specified, and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within a participants. The treatment group to which participants were randomized will be used in the listings.

For randomized participants, age (in years) collected on the Day 1 visit will be used for analyses and presentation in listings. For screen failures, age calculated on the date of the informed consent was signed will be used. Because only birth year is collected on the eCRF, "01 July" will be used for the unknown birth day and month for the purpose of age calculation.

In general, permanent discontinuation of study drug refers to premature discontinuation of study drug or completion of study drug.

3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. Participants included in each analysis set will be determined before database finalization. The analysis set will be included as a subtitle of each table, figure, and listing. A summary of the number and percentage of participants in each analysis set will be provided by treatment group and in total.

3.1.1. All Randomized Analysis Set

The **All Randomized Analysis Set** will include all participants who were randomized into the study. This is the primary analysis set for by-subject listings.

3.1.2. B/F/TAF Full Analysis Set

The **B/F/TAF Full Analysis Set (FAS)** will include all participants who (1) are randomized into the study, (2) have received at least 1 dose of B/F/TAF study drug, and (3) do not have pre-existing INSTI resistance-associated mutations (based on historical data). Participants will be grouped according to the treatment to which they were randomized. For the B/F/TAF FAS, all efficacy data, including data collected after the last dose of study drug, will be included, unless specified otherwise.

This is the primary analysis set for efficacy analyses.

3.1.3. B/F/TAF Safety Analysis Set

The **B/F/TAF Safety Analysis Set** will include all participants who (1) are randomized into the study and (2) have received at least 1 dose of B/F/TAF study drug. All data collected up to 30 days after participants permanently discontinue study drug will be included in safety summaries, unless specified otherwise.

This is the primary analysis set for safety analyses.

3.2. Subject Grouping

Participants will be grouped into the following 3 groups:

- B/F/TAF: this group includes all participants randomized to the B/F/TAF group and who received at least 1 dose of B/F/TAF
- Delayed Switch to B/F/TAF: this group includes all participants randomized to the SBR group who switched to B/F/TAF at Week 24 and received at least 1 dose of B/F/TAF
- All B/F/TAF: all participants who received at least one dose of study assigned B/F/TAF (both immediate and delayed switch to B/F/TAF).

3.3. Strata and Covariates

Randomization was stratified by the baseline third agent ARV class at study entry (INSTI, NNRTI, PI or CCR5 antagonist).

If there are discrepancies in stratification factor values between the interactive web response system (IWRS) and the clinical database, the values recorded in the clinical database will be used to group participants for analyses.

3.4. Examination of Subject Subgroups

3.4.1. Subject Subgroups for Efficacy Analyses

No subgroup analyses for efficacy are planned for the final analysis.

3.4.2. Subject Subgroups for Safety Analyses

1) Incidence of all treatment-emergent AEs (TEAEs) will be analyzed for the following subject subgroups (also see Section 7.1.6):
   - Age (years): (a) < 50 and (b) ≥ 50
   - Sex at birth: (a) male and (b) female
2) Renal-related laboratory tests (ie, serum creatinine and $eGFR_{CG}$) will be analyzed for the following subgroups:
   - Baseline ARV Medication containing any of the following: rilpivirine (RPV), dolutegravir (DTG), ritonavir (RTV), cobicistat
   - Baseline ARV Medication not containing any of the following: RPV, DTG, RTV, cobicistat

3) Fasting metabolic laboratory tests will be analyzed for the following subgroups:

- Baseline ARV Medication containing TAF
- Baseline ARV Medication containing TDF
- Baseline ARV Medication not containing any of the following: TAF, TDF
- Baseline ARV Medication containing efavirenz (EFV)
- Baseline ARV Medication not containing EFV

4) Selected safety endpoints may be analyzed for the following subject subgroups (see Section 8.1 for details):

- Participants with HIV/HBV coinfection at baseline
- Participants with incident HIV/HBV coinfection while on study drug (if any)

5) Selected safety endpoints will be analyzed for the following subject subgroups (see Section 8.2 for details):

- Participants with HIV/HCV coinfection at baseline
- Participants with incident HIV/HCV coinfection while on study drug (if any)

3.5. Multiple Comparisons

No prespecified multiplicity adjustments are planned for confidence intervals (CIs) or statistical tests.

3.6. Missing Data and Outliers

3.6.1. Missing Data

A missing datum for a given study analysis window may be due to any of the following reasons:

- A visit occurring in the window, but data were not collected or were unusable
- A visit not occurring in the window
- A participant prematurely discontinuing from the study before reaching the window

In general, values for missing data will not be imputed, unless methods for handling missing data are specified.

For missing last dosing date of study drug, imputation rules are described in Section 3.8.1. The handling of missing or incomplete dates for adverse event onset is described in Section 7.1.5.2, and for concomitant non-ARV medications in Section 7.4.2.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be done to evaluate the impact of outliers on efficacy or safety outcomes, unless specified otherwise. All data will be included in the analyses.

3.7. Data Handling Conventions and Transformations

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed as follows:

- A value that is 1 unit less than the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "< x" (where x is considered the limit of quantitation). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used for calculation of summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used for calculation of summary statistics.
- A value that is 1 unit above the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "> x" (where x is considered the limit of quantitation). Values with decimal points will follow the same logic as above.
- The limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the limit of quantitation).

Logarithmic (base 10) transformations will be applied to HIV-1 RNA data for efficacy analyses. HIV-1 RNA results of 'No HIV-1 RNA detected' and "<20 cp/mL HIV-1 RNA Detected" will be imputed as 19 copies/mL for analysis purposes.

3.8. Analysis Windows

3.8.1. Definition of Study Day

Study Day 1/First Dose Date is defined as the day when the first dose of B/F/TAF was taken. The first dose date is the earliest nonmissing start date of B/F/TAF study drug recorded on the Study Drug Administration eCRF.

Study Days are calculated relative to Study Day 1. For events that occur on or after the Study Day 1 date, study days are calculated as (visit date minus Study Day 1 date plus 1). For events that occurred prior to Study Day 1, study days are calculated as (visit date minus Study Day 1 date).

Last Dose Date is defined as the maximum, nonmissing end date of B/F/TAF recorded on the Study Drug Administration eCRF and "Study Drug Permanently Discontinued" box checked for participants who prematurely discontinued study drug or completed study drug according to the Study Drug Completion eCRF.

For partial or missing last dose dates, please refer to the programming specifications for imputation rule details.

Last Study Date is the latest of the study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date, for participants who prematurely discontinued study according to the Study Completion eCRF.

Baseline value is defined as the last value obtained on or prior to Study Day 1 for all assessments.

Note: for first dose date for SBR treatment group for listings, refer to the Week 48 SAP.

3.8.2. Analysis Windows

Participant visits might not occur on protocol specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

The analysis windows for HIV-1 RNA, hematology, chemistry, urinalysis, urine pregnancy laboratory tests, $eGFR_{CG}$, vital signs, and weight are presented in Table 3-1.

Table 3-1. Analysis Windows for HIV-1 RNA, Hematology, Chemistry, Urinalysis, Urine Pregnancy Laboratory Tests, $eGFR_{CG}$, Vital Signs and Weight

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	56
Week 12	84	57	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630

The analysis windows for CD4+ cell count, CD4 %, and metabolic assessments (including fasting glucose and lipid panel: total cholesterol, high density lipoprotein [HDL], direct low density lipoprotein [LDL], triglycerides, and total cholesterol to HDL ratio are presented in Table 3-2.

Table 3-2. Analysis Windows for CD4+ cell count, CD4 %, and Metabolic Assessments

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline	1		1
Week 24	168	2	252
Week 48	336	253	420
CCI			

The analysis windows for plasma HBV DNA are presented in Table 3-3.

Table 3-3. Analysis Windows for Plasma HBV DNA

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline	1		1
Week 24	168	2	252
Week 48	336	253	420

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Window

Depending on the statistical analysis method, single values are required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time to event analysis would not require one value per analysis window. When a single value is needed, the following rule(s) will be used.

If multiple nonmissing numeric observations exist in a window, then records will be chosen as follows:

- For baseline, the latest available record on or prior to the first dose date of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, average will be used for the baseline value, except for HIV-1 RNA (see below).

- For postbaseline visits:

  For CD4+ cell count, CD4%, and HBV DNA, the record(s) collected on the latest day in the window will be selected for analysis.

  For other numeric observations (ie, except HIV-1 RNA, CD4+ cell count, CD4%, and HBV DNA), the record(s) collected on the day closest to the nominal day for that visit will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.

  For any numeric observations except HIV-RNA, if there are multiple records on the selected day, the average will be taken.

- For baseline and postbaseline HIV-1 RNA, the latest (considering both date and time) record(s) in the window will be selected. If both "HIV RNA Taqman 2.0" and "HIV RNA Repeat" (ie, the HIV-1 RNA result obtained from an additional aliquot of the original sample) are available with the same collection time, the results from the "HIV RNA Repeat" will be selected for analysis purposes; otherwise, if there are multiple "HIV RNA Taqman 2.0" records with the same collection time, the geometric mean will be taken for analysis purposes.

If multiple valid nonmissing categorical observations exist in a window, records will be chosen as follows:

- For baseline, the last available record on or prior to the first dose date of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected.

- For postbaseline visits, the most conservative value within the window will be selected.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

4.1.1. Subject Enrollment

The number and percentage of participants randomized at each investigator site will be summarized by treatment group (B/F/TAF and Delayed Switch to B/F/TAF) and overall using the B/F/TAF safety analysis set. The denominator for this calculation will be the number of participants in the B/F/TAF safety analysis set. Similarly, the number and percentage of participants enrolled in each randomization stratum will be summarized based on reclassified strata using the baseline third agent ARV class based on the Non-Study ARV Medication eCRF.

If there are discrepancies between IWRS and collected data with regard to stratum assignment, a listing of the discrepancies will be provided.

4.1.2. Subject Disposition

The summary of subject disposition will be provided by treatment group (B/F/TAF and Delayed Switch to B/F/TAF) and overall for all screened participants. This summary will include the number of participants screened, screen failure participants who were not randomized, participants who met all eligibility criteria and were not randomized, participants randomized, participants randomized but never treated, participants with delayed switch to B/F/TAF, participants in the B/F/TAF safety analysis set, and the number of participants in the B/F/TAF FAS.

In addition, the number and percentage of the participants in the following categories will be summarized:

- Completed study drug
- Prematurely discontinuing study drug (with summary of reasons for discontinuing study drug)
- Treated in the Extension phase
- Completed study
- Prematurely discontinuing from study (with summary of reasons for discontinuing study).

The denominator for the percentages of participants in each category will be the number of participants in the B/F/TAF safety analysis set.

No inferential statistics will be generated. A data listing of reasons for study drug/study discontinuation will be provided.

4.2. Extent of Study Drug Exposure and Adherence

4.2.1. Duration of Exposure to Study Drug

Duration of exposure will be calculated for the B/F/TAF and Delayed Switch to B/F/TAF groups. Duration of exposure to study drug will be defined as (last dose date - first dose date + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

Duration of exposure to study drug will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of participants exposed for specified periods, eg, ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 12 weeks (84 days), ≥ 24 weeks (168 days), ≥ 36 weeks (252 days), ≥ 48 weeks (336 days), ≥ 60 weeks (420 days), ≥ 72 weeks (504 days).

Summaries will be provided for participants in the B/F/TAF safety analysis set. No inferential statistics will be provided.

4.2.2. Adherence to Study Drug Regimen

Study drug regimen adherence will be computed based on pill counts. The numbers of pills of study drug dispensed and returned are captured on study drug accountability eCRF.

Adherence (%) of study drug regimen will be calculated as follows:

$$\text{Adherence (\%)} \quad 100 \times \frac{\text{Total No. of pills taken}}{\text{Total No. of pills prescribed}}$$

$$100 \times \frac{\sum\sum \text{No. of pills taken at each dispensing period}^{[1]}}{\sum\sum \text{No. of pills prescribed at each dispensing period}^{[2]}}$$

[1] Number of pills taken at a distinct dispensing period for a study drug is calculated as the minimum of (a) the daily number of pills prescribed for the study drug multiplied by the duration of treatment at the dispensing period, and (b) the number of pills taken for the study drug (number of pills dispensed minus the number of pills returned). Total number of pills taken is determined by summing the number of pills taken for each study drug contained in the study drug regimen from all evaluable dispensing periods.
[2] Number of pills prescribed at a distinct dispensing period for a study drug is calculated as the daily number of pills prescribed for the study drug multiplied by the duration of treatment at the dispensing period. Total number of pills prescribed is determined by summing the number of pills prescribed for each study drug contained in the study drug regimen from all evaluable dispensing periods.

The duration of treatment at a dispensing period for a study drug is calculated as the minimum of (a) the last returned date of study drug at a dispensing period, (b) date of premature discontinuation of the study drug, and (c) next pill dispensing date of the study drug, minus dispensing date of the study drug.

The next pill dispensing date is the following dispensing date of the study drug regardless of the bottle return date.

For a record where the number of pills returned was missing (with "Yes" answered for "Was Bottle returned?" question), it is assumed the number of pills returned was zero. If the number of pills dispensed was missing or any study drug bottle was not returned or the bottle return status was unknown, then all records in that dispensing period for that study drug will be excluded from both denominator and numerator calculation.

Adherence will be calculated using all data from the entire dosing period up to the date of permanent discontinuation of the study drug for participants who prematurely discontinued study drug or completed study drug.

Descriptive statistics for adherence (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of participants belonging to adherence categories (eg, < 80%, ≥ 80% to < 90%, ≥ 90% to < 95%, ≥ 95%) will be provided for participants who return at least 1 bottle and have calculable adherence during the study in the B/F/TAF safety analysis set. No inferential statistics will be provided.

4.3. Protocol Deviations

A listing will be provided for all participants who violated at least 1 inclusion or exclusion criterion. The listing will include the criteria not met.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations by deviation reason and the total number of important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group (B/F/TAF and Delayed Switch to B/F/TAF) for the B/F/TAF FAS. A by-subject listing will be provided for those participants with important protocol deviations.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (2019 nCOV [COVID-19]) pandemic which caused a disruption in the regular visit schedules for this study. Some participants were unable to attend onsite visits due to shelter in place guidelines, site closures or other reasons. Visits related to the primary and secondary endpoints of the study were not impacted.

4.4.3. Missed and Virtual Visits due to COVID-19

An overall summary of the number and percentage of participants with missed or virtual visits (e.g., at least 1, with 1, 2, 3 or more visits) due to the COVID-19 pandemic will be provided. The denominator for the percentage calculation will be the total number of participants in the B/F/TAF safety population.

A by-subject listing will be provided presenting participants who missed or had virtual visits due to COVID-19. The determination of missing or virtual visits due to COVID-19 was done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Appendix 5.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic data (eg, age, sex at birth, gender identity, sexual orientation, race, and ethnicity) and baseline characteristics (eg, body weight, height, and body mass index [BMI]) will be summarized by treatment group (B/F/TAF and Delayed Switch to B/F/TAF) and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percentage of participants for categorical data. The summaries of demographic data and baseline subject characteristics will be provided for the B/F/TAF safety analysis set.

5.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized by treatment group (B/F/TAF and Delayed Switch to B/F/TAF) and overall using descriptive statistics:

- HIV-1 RNA categories (copies/mL): (a) < 50, (b) ≥ 50
- CD4+ cell count (/μL)
- CD4+ cell count categories (/μL): (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500
- CD4 percentage (%)
- Mode of infection (HIV risk factors)
- HIV disease status
- $eGFR_{CG}$ (mL/min)
- HIV/HBV co-infection status (Yes/No/Missing, see Section 8.1 for definition)
- HIV/HCV co-infection status (Yes/No/Missing, see Section 8.2 for definition)
- Duration of HIV Diagnosis (years) (calculated as years prior to year from First Dose/Day 1 date; see programming specifications)
- Duration of HIV Treatment (Years) (calculated as years prior to year from First Dose/Day 1 date; see programming specifications)
- Duration of baseline ARV medication prior to randomization (based on the Non-Study ARV Medication eCRF, see programming specifications)

- Baseline ARV Regimen (based on the Non-Study ARV Medication eCRF, see programming specifications)

  Baseline ARV Medication Backbone (FTC+TAF, FTC+TDF, TDF+3TC, ABC+3TC, AZT+3TC)

  Baseline 3rd agent (INSTI, NNRTI, PI, CCR5), and further broken down by ingredient

  Baseline ARV Medication (Backbone+3rd agent)

5.3. Medical History

General medical history data will be collected at screening and listed only. General medical history data will not be coded.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the US FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}.

The analyses of the primary efficacy endpoint were performed in the Week 24 analysis, and will not be repeated here.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of the Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm
- The proportion of participants with HIV-1 RNA < 50 copies/mL at Week 24 and Week 48 as determined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4+ cell count at Week 24 and Week 48

The analyses of the secondary efficacy endpoints were performed in the Week 24 and Week 48 analyses and will not be repeated here.

CCI [redacted]

6.4. Changes from Protocol-Specified Efficacy Analyses

No change from the protocol-specified efficacy analyses are planned.

7. SAFETY ANALYSES

Safety data will be summarized for the participants in the B/F/TAF safety analysis set. All safety data collected up to 30 days after permanent discontinuation of B/F/TAF study will be summarized by treatment group, unless specified otherwise. All safety data will be included in data listings.

7.1. Adverse Events and Deaths

Summaries of AEs by treatment group (B/F/TAF, Delayed Switch to B/F/TAF, All B/F/TAF) will include data collected up to 30 days after permanent discontinuation of study drug.

7.1.1. Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lowest-level term (LLT) will be provided in the AE dataset

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) or Grade 4 (life threatening) according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be left as "missing" for data listings.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE eCRF to the question of "Related to Study Treatment." Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety (GLPS) Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the B/F/TAF study drug start date and no later than 30 days after permanent discontinuation of the B/F/TAF study drug, or
- Any AEs leading to premature discontinuation of B/F/TAF study drug.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The month and year (or year) of the AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The month and year (or year) of the AE onset is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date marked as ongoing or on or after the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Death

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, HLT, PT, and treatment group (B/F/TAF, Delayed Switch to B/F/TAF, and All B/F/TAF). For other AEs described below, summaries will be provided by SOC, PT, and treatment group (B/F/TAF, Delayed Switch to B/F/TAF, and All B/F/TAF) using the B/F/TAF safety analysis set:

- Any Grade 2, 3, or 4 treatment-emergent AEs
- Any Grade 3 or 4 treatment-emergent AEs
- All treatment-emergent study drug-related AEs
- Any Grade 2, 3, or 4 treatment-emergent study drug-related AEs
- Any Grade 3 or 4 treatment-emergent study drug-related AEs
- All treatment-emergent SAEs
- All treatment-emergent study drug-related SAEs
- All treatment-emergent AEs that caused premature discontinuation from study drug

A brief, high-level summary of AEs described above will be provided by treatment group (B/F/TAF, Delayed Switch to B/F/TAF, and All B/F/TAF) and by the number and percentage of participants who experienced the above AEs. Treatment-emergent deaths observed in the study will be also included in this summary.

Treatment-emergent death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and HLT within each SOC (if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all treatment-emergent AEs, Grade 3 or 4 treatment-emergent AEs, treatment-emergent study drug-related AEs, Grade 2, 3, or 4 treatment-emergent study drug-related AEs, and treatment-emergent SAEs will be summarized by PT only, in descending order of total frequency.

Summary of treatment-emergent AEs by SOC and PT will also be conducted for all subgroups listed in Section 3.4.2.

By-participant listings will be provided for all AEs, study drug-related AEs, grade 3 and 4 AEs, serious AEs, study drug-related SAEs, and AEs leading to premature study drug discontinuation.

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Stage 3 Opportunistic Illnesses in HIV

On an ongoing basis, AEs will be reviewed for events that might meet the definition of stage 3 opportunistic illnesses in HIV that are indicative of an AIDS-defining diagnoses (see Protocol Appendix 6). The Gilead medical monitor will review the possible stage 3 opportunistic illnesses and approve the events that meet the definition. Events that meet the stage 3 opportunistic illness definition of an AIDS-Defining Diagnosis will be listed.

7.1.7.2. Cardiovascular or Cerebrovascular Events

Preferred terms for cardiovascular or cerebrovascular events are from relevant Standardised MedDRA Query (SMQ). The selected PT listing was provided by Gilead GLPS and reviewed by Gilead medical monitors (see details in Appendix 3).

The number and percentage of participants with treatment-emergent cardiovascular or cerebrovascular events and serious cardiovascular or cerebrovascular events by PT will be summarized by treatment group (B/F/TAF, Delayed Switch to B/F/TAF, and All B/F/TAF) based on the B/F/TAF safety analysis set. A by-subject data listing of cardiovascular or cerebrovascular events will be provided.

7.1.7.3. Hepatic Events

Preferred terms for hepatic events are from 15 relevant SMQs, which are identified as non-infectious and non-congenital hepatobiliary disorders. The selected PT listing was provided by Gilead GLPS and reviewed by Gilead medical monitors (see details in Appendix 4).

The number and percentage of participants with treatment-emergent hepatic events and serious hepatic events by PT will be summarized by treatment group (B/F/TAF, Delayed Switch to B/F/TAF, and All B/F/TAF) based on the B/F/TAF safety analysis set. A by-subject data listing of hepatic events will be provided.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the B/F/TAF safety analysis set and will include data collected up to the last dose of B/F/TAF study drug plus 30 days.

The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group (B/F/TAF, Delayed Switch to B/F/TAF) for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline at each postbaseline analysis window

A baseline laboratory value will be defined as the last nonmissing value obtained on or prior to the date of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

Calcium Corrected for Albumin

Calcium corrected for albumin will be calculated and summarized for the study. The following formula will be used when both serum calcium and albumin results for a given blood drawn are available and serum albumin value is < 4.0 g/dL.

- Calcium corrected for albumin (mg/dL) serum calcium (mg/dL) + 0.8 × (4.0 - albumin (g/dL)).

Toxicity grading for calcium will be applied based on the corrected values.

Estimated GFR

The Cockcroft-Gault (CG) formula will be used to calculate $eGFR_{CG}$:

- $eGFR_{CG}$ (mL/min) [(140 age (yrs)) × weight (kg) × (0.85 if female)] / (SCr (mg/dL) × 72), where weight is total body mass in kilograms, and SCr is serum creatinine.

7.2.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be used for assigning toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

If there is any laboratory toxicity grading scale overlapping with the normal reference ranges (eg, grade 1 scale overlaps with normal reference ranges), laboratory values that are within the normal range will be grade 0 except for lipid tests.

For triglycerides, LDL, and cholesterol, the protocol specified toxicity grading scale is for fasting test values, so non-fasting lipid results (or lipid results without known fasting status) will not be graded or summarized by toxicity grades.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to the cutoffs specified at the start of Section 7.2.

If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

Fasting glucose and nonfasting glucose (including glucose results without a known fasting status) are graded based on different grading scales as specified in the protocol. Most participants had a nonfasting glucose at the Screening visit and a fasting glucose at the Day 1 visit; therefore, both a baseline nonfasting glucose and a baseline fasting glucose are available for most participants, and treatment-emergent laboratory abnormalities will be summarized for both nonfasting glucose and fasting glucose.

Both urine RBC based on microscopic examination, labeled as Hematuria (Quantitative), and urine blood based on a dipstick, labeled as Hematuria (Dipstick), are assessed and assigned a toxicity grade in this study. Hematuria (Quantitative) is a reflex test. Urine RBC based on microscopic examination or Dipstick will be presented in laboratory toxicity summary tables and listings.

7.2.2.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group (B/F/TAF, Delayed Switch to B/F/TAF, and All B/F/TAF); participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 and 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with any nonmissing postbaseline values for the particular laboratory test.

A by-subject listing of all treatment-emergent laboratory abnormalities and treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order.

7.2.3. Metabolic Laboratory Evaluations

For metabolic assessments, including fasting glucose and the lipid panel (ie, total cholesterol, triglycerides, LDL, HDL, total cholesterol to HDL ratio); only those measurements under fasting status will be summarized for the B/F/TAF and Delayed Switch to B/F/TAF groups.

In addition, the number and percentage of participants who took lipid modifying medications at baseline and initiated the medications during the study will be provided for the B/F/TAF and Delayed Switch to B/F/TAF treatment groups.

A lipid modifying medication is defined as a medication with drug class (based on World Health Organization [WHO] Drug ATC2 term) “LIPID MODIFYING AGENTS” and WHO Drug preferred drug name containing the wording of “STATIN”.

A sensitivity analysis of fasting lipid tests will be performed by excluding participants who took lipid modifying medications at baseline or initiated the medications during the study: baseline values, Week 72 values, and changes from baseline at Week 72 will be summarized for the B/F/TAF group using descriptive statistics. Only participants with both baseline and Week 72 values will be included in the analysis. A similar summary at Week 48 will be produced for the Delayed Switch to B/F/TAF group.

Summary of baseline, postbaseline, and change from baseline in fasting metabolic laboratory tests will be repeated within each subgroup of baseline ARV medication (see Section 3.4.2).

Median (Q1, Q3) of change from baseline in fasting metabolic assessments over time will be plotted by treatment group (B/F/TAF and Delayed Switch to B/F/TAF).

7.2.4. Liver-Related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized for the B/F/TAF, Delayed Switch to B/F/TAF, and All B/F/TAF groups using the number and percentage of participants who were reported to have the following laboratory test values for post baseline measurements:

- Aspartate aminotransferase (AST): (a) > 3 × Upper limit of normal (ULN), (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- Alanine aminotransferase (ALT): (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- AST or ALT: (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- Total bilirubin: (a) > 1 × ULN, (b) > 2 × ULN
- Alkaline phosphatase (ALP) > 1.5 × ULN
- AST or ALT > 3 × ULN and total bilirubin: (a) > 1.5 × ULN, (b) > 2 × ULN
- AST or ALT > 3 × ULN and total bilirubin > 2 × ULN and ALP < 2 × ULN

For individual laboratory tests, participants will be counted once based on the most severe postbaseline value. For both the composite endpoint of AST or ALT and total bilirubin, and the composite endpoint of AST or ALT, total bilirubin, and ALP, participants will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of participants in the B/F/TAF safety analysis set with nonmissing postbaseline value of the tests in evaluation at the same postbaseline visit date.

Participants with AST or ALT > 3 × ULN, total bilirubin > 1 x ULN, or ALP > 1.5 x ULN while on-treatment will also be listed.

In addition, baseline, postbaseline, and change from baseline in AST, ALT, ALP, and total bilirubin will be summarized by treatment group (B/F/TAF and Delayed Switch to B/F/TAF) and visit using descriptive statistics.

In addition, ALT elevation (ie, ALT > 2 x Baseline and ALT > 10 x ULN) and ALT flare, defined as ALT elevations confirmed at two consecutive visits, will be evaluated and listed for participants with HIV/HBV coinfection at baseline. The first occurrence of two or more consecutive ALT elevations will be identified as the ALT flare.

7.2.5. Renal-Related Laboratory Evaluations

7.2.5.1. Serum Creatinine and $eGFR_{CG}$

Baseline, postbaseline, and change from baseline in serum creatinine and $eGFR_{CG}$ will be summarized by treatment group (B/F/TAF and Delayed Switch to B/F/TAF) and visit using descriptive statistics.

Median (Q1, Q3) of change from baseline in serum creatinine and $eGFR_{CG}$ over time will be plotted by treatment group.

Summary of baseline, postbaseline, and change from baseline in serum creatinine and $eGFR_{CG}$ will be repeated within each subgroup of baseline ARV medication (see Section 3.4.2).

7.2.5.2. Proteinuria by Urinalysis (Dipstick)

The proteinuria by urinalysis (dipstick) toxicity grade (Grade 0 to Grade 3) will be summarized by baseline proteinuria toxicity grade and treatment group (B/F/TAF and Delayed Switch to B/F/TAF) by visit. In addition, the last on-treatment proteinuria toxicity grade will be summarized by baseline proteinuria toxicity grade and treatment group. On-treatment data is as all data collected up to 1 day after permanent discontinuation of study drug.

7.3. Body Weight, Height, and Vital Signs

Descriptive statistics will be provided by treatment group (B/F/TAF and Delayed Switch to B/F/TAF) for vital signs and body weight as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline to each postbaseline analysis window

A baseline value will be defined as the last nonmissing value obtained on or prior to the date of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order. In the same listing, a by-subject listing of body weight, height, and BMI will be provided.

7.4. Prior and Concomitant Medications

7.4.1. Nonstudy Drug Antiretroviral Medications

Any nonstudy drug antiretroviral (ARV) medications used prior to, during, or after the study (if collected) will be coded using the Gilead-modified WHO Drug Dictionary for ARV medications. The WHO preferred drug name and drug code will be attached to the clinical database. All nonstudy drug ARV medications will be listed.

7.4.2. Concomitant Non-ARV Medications

Concomitant non-ARV medications (ie, medications other than study drug that are taken while receiving study drug) will be coded using the WHO Drug Dictionary. The WHO Drug preferred drug name and drug code will be attached to the clinical database. Use of concomitant medications from the date of first dose of study treatment up to the date of last dose of study treatment will be summarized (number and percentage of participants) by treatment group (B/F/TAF and Delayed Switch to B/F/TAF) and preferred drug name. Multiple drug use will be counted only once per participant for each preferred drug name. The summary will be sorted by decreasing total frequency. For drugs with the same frequency, sorting will be done alphabetically.

If the start or stop date of non-ARV medications is incomplete, the month and year (or year alone if month is not recorded) of the start or stop date will be used to determine whether the non-ARVs are concomitant or not. The medication is concomitant if the month and year of the start or stop (or year of the start or stop, if month is not recorded) of the medication does not meet either of the following criteria:

- The month and year of start of the medication is after the date of the last dose of study drug
- The month and year of stop of the medication is before the date of the first dose of study drug

If the start and stop date of non-ARV medications are complete, the start date is not after last dose date and the stop date is not before first dose date, or the non-ARV medications are marked as ongoing and start date is on or before last dose date, the non-ARV medications are concomitant.

Summaries of non-ARV concomitant medications will be provided for the B/F/TAF safety analysis set. Participants with any non-ARV concomitant medications will be listed. No inferential statistics will be provided.

7.5. Electrocardiogram Results

A by-subject listing for electrocardiogram (ECG) assessment results will be provided.

7.6. Other Safety Measures

A data listing will be provided for participants experiencing pregnancy during the study. Physical examination data was not collected in the eCRF. Therefore, it will not be included in the analysis.

7.7. Subject Subgroup for Safety Endpoints

Incidence of all treatment-emergent AEs will be repeated within each subgroup defined in Section 3.4.2 using the B/F/TAF safety analysis set.

7.8. Changes from Protocol-Specified Safety Analyses

No changes from the protocol-specified safety analyses are planned.

8. SPECIAL POPULATION ANALYSES

8.1. Analyses for HIV/HBV Coinfected Participants

Participants with HIV/HBV coinfection at baseline are defined as participants who meet any of the following two criteria:

- Positive HBsAg on or prior to the first dose date, or
- Negative HBsAg, negative HBsAb, positive HBcAb, and quantifiable HBV DNA (ie, HBV DNA ≥ 20 IU/mL) on or prior to the first dose date.

The following analyses will be conducted by treatment (B/F/TAF, and Delayed Switch to B/F/TAF) for participants with HIV/HBV coinfection at baseline:

- Treatment-emergent adverse events overall summary
- Treatment-emergent adverse events by SOC, HLT, and PT
- Treatment-emergent laboratory abnormalities
- The change from baseline for liver-related laboratory tests, including ALT, AST, ALP, total bilirubin, direct and indirect bilirubin.

Listings will be provided for:

- adverse events
- liver-related laboratory tests and HBV DNA results
- ALT elevation (ie, ALT > 2 x Baseline and ALT > 10 x ULN) and ALT flare (see section 7.2.4)

Participants with incident HIV/HBV coinfection while on study drug are defined as participants who are not HIV/HBV coinfected at baseline and meet any of the following criteria:

- Positive HBsAg after the first B/F/TAF dose date and on or prior to the last B/F/TAF dose date, or
- Negative HBsAg, negative HBsAb, positive HBcAb, and quantifiable HBV DNA (ie, HBV DNA ≥ 20 IU/mL) after the first B/F/TAF dose date and on or prior to the last B/F/TAF dose date, or

- Experience any of the following adverse events (ie, selected MedDRA PTs from the SMQ of "Liver Infections") with onset date after the first B/F/TAF dose date and on or prior to the last B/F/TAF dose date: Acute hepatitis B, Chronic hepatitis B, Congenital hepatitis B infection, Hepatitis B, Hepatitis B core antibody positive, Hepatitis B DNA assay positive, Hepatitis B surface antigen positive, Hepatitis B virus test positive.

The following listings will be provided for participants with incident HIV/HBV coinfection while on study drug:

- Listing of adverse events
- Listing of liver-related laboratory tests and HBV DNA results

8.2. Analyses for HIV/HCV Coinfected Participants

Participants with HIV/HCV coinfection at baseline are defined as participants with positive HCVAb and quantifiable HCV RNA (ie, HCV RNA ≥ 15 IU/mL) on or prior to the first dose date. The following listings will be provided for participants with HIV/HCV coinfection at baseline:

- Listing of adverse events
- Listing of liver-related laboratory tests and HCV RNA results

Participants with incident HIV/HCV coinfection while on study drug are defined as participants who are not HIV/HCV coinfected at baseline and meet any of the following criteria:

- Positive HCVAb after the first B/F/TAF dose date and on or prior to the last B/F/TAF dose date, or
- Quantifiable HCV RNA (ie, HCV RNA ≥ 15 IU/mL) after the first B/F/TAF dose date and on or prior to the last B/F/TAF dose date, or
- Experience any of the following adverse events (ie, selected MedDRA PTs from the SMQ of "Liver Infections") with onset date after the first B/F/TAF dose date and on or prior to the last B/F/TAF dose date: Acute hepatitis C, Chronic hepatitis C, Hepatitis C, Hepatitis C antibody positive, Hepatitis C RNA positive, Hepatitis C virus test positive.

The following listings will be provided for participants with incident HIV/HCV coinfection while on study drug:

- Listing of adverse events
- Listing of liver-related laboratory tests and HCV RNA results

9. PATIENT REPORTED OUTCOMES

The patient-reported outcomes were analyzed for the Week 48 analysis, and the analyses will not be repeated for the final analysis.

10. REFERENCES

DeJesus E, Villanueva J, Lopez J, Brinson C, Crofoot G, Daar ES, et al. Tenofovir Alafenamide vs Tenofovir Disoproxil Fumarate in Hispanic/Latinx and Black Participants: Efficacy, Bone and Renal Safety Results From a Pooled Analysis of 7 Clinical Trials [Poster 318]. IDWeek; 2019 2-6 October; Washington, DC.

U. S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. Guidance for Industry. Silver Spring, MD. November, 2015.

11. SOFTWARE

SAS® Version 9.4 (SAS Institute Inc., Cary, NC.) is to be used for all programming of tables, listings, and figures.

PASS Version 14 (NCSS, LLC, Kaysville, Utah) was used for planned sample size and power calculation.

12. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

13. APPENDICES

Appendix 1. Study Procedures Table

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]						Post Week 48[e]	30 Day Follow-Up[f]	ESDD[g]
			4	12	24	28[d]	36	48	Every 12 Weeks[cc]		
Informed Consent	X										
HIV Symptoms Distress Module		X	X		X	X		X			
HIV-TSQ[h]		X	X		X						
VAS Adherence Questionnaire[i]		X	X	X	X						
Medical History	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Complete/Symptom-Directed Physical Exam[j]	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG (performed supine)	X										
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[k]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[l]		X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[l]	X										
FSH Test[m]	X										
Chemistry Profile[n]	X	X	X	X	X	X	X	X	X	X	X
Metabolic Assessments[o]		X			X			X	X		
Estimated GFR	X	X	X	X	X	X	X	X	X	X	X

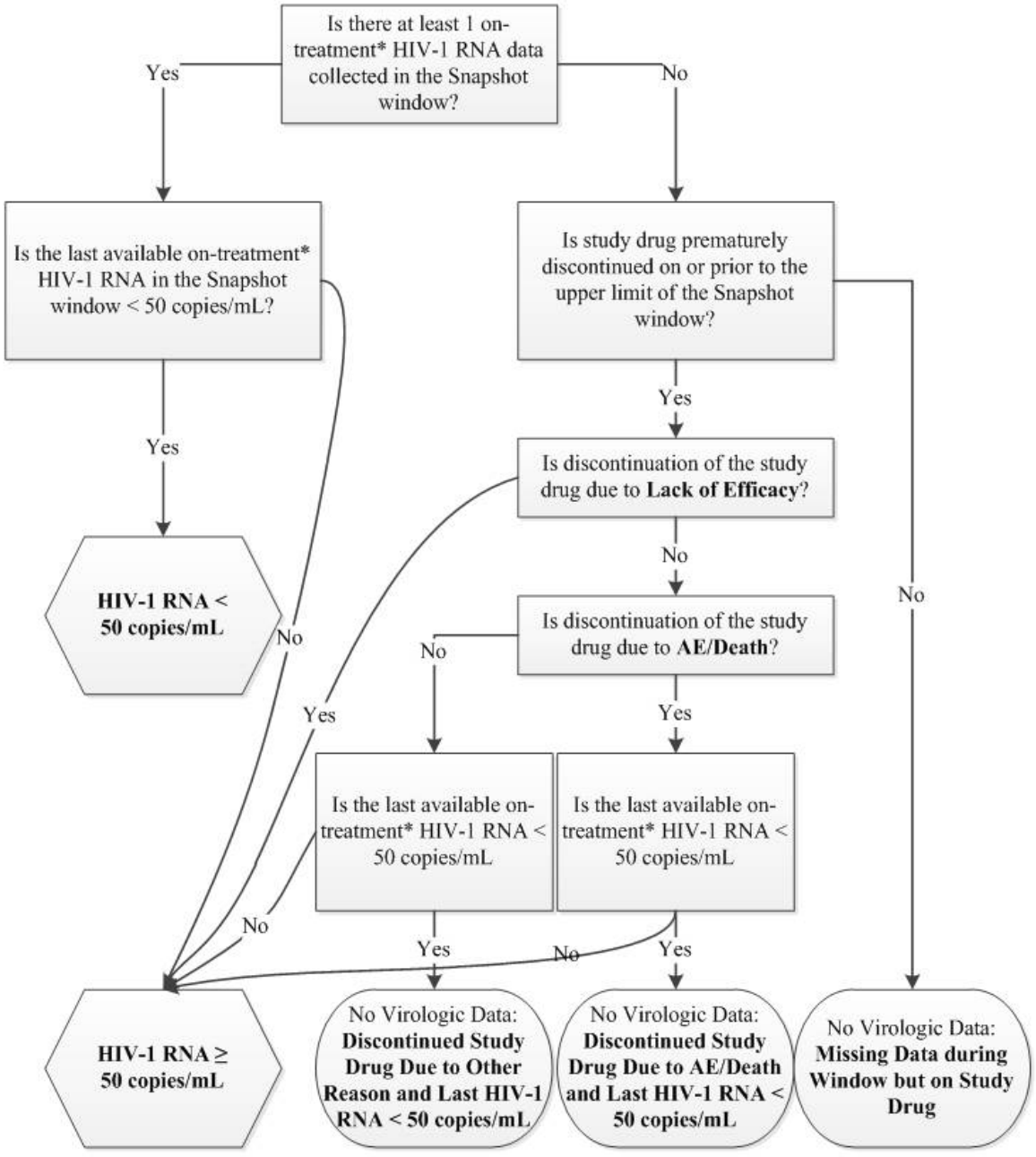
Study Procedure	Screening[a]	Day 1[b]	End of Week[c]						Post Week 48[e]	30 Day Follow-Up[f]	ESDD[g]
			4	12	24	28[d]	36	48	Every 12 Weeks[cc]		
Hematology Profile[p]	X	X	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA[q]	X	X	X	X	X	X	X	X	X	X	X
CCI											
HBV Blood Panel[s]	X[t]							X[t]			
Plasma HBV DNA[u]		X			X			X			X
HCV Serology[v]	X							X	X		
HIV-1 Genotype/Phenotype[q]											X[q]
Plasma, Serum, and Urine Sample Storage[w]		X	X	X	X	X	X	X	X		X
Whole Blood for HIV-1 DNA archive testing		X			X[x]						
CCI											
Obtain Screening Number	X										
Randomization[z]		X									
Study Drug Dispensation		X[bb]	X[bb]	X[bb]	X[aa]	X	X	X	X		
Study Drug Accountability			X[bb]	X[bb]	X	X	X	X	X		X

a Evaluations to be completed within 30 days prior to Day 1.
b Participants should initiate dosing of study drug on the same day as the Day 1 visit.
c All study visits are to be completed ± 6 days of the protocol specified visit date (based on the Day 1 visit), unless otherwise specified.
d Participants randomized to continue their baseline regimen will have an additional visit at Week 28.
e At the study Week 48 Visit, participants who wish to continue on B/F/TAF will be given the option to receive FDC of B/F/TAF for up to an additional 24 weeks or until they have access to FDC of B/F/TAF, whichever occurs first, and attend study visits every 12 weeks (± 6 days of the protocol specified visit date) followed by a 30 Day Follow Up Visit.
f Must be completed 30 days after discontinuing study drug. For the purpose of scheduling a 30 Day Follow Up Visit, a ± 6 days window may be used. Required for participants who permanently discontinue study drug prior to Week 48 and do not continue in the study through at least one subsequent visit after the ESDD visit. Participants who participate post Week 48 will be required to return to the clinic 30 days after the completion of study drugs for the 30 Day Follow Up Visit.
g Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Participants will be asked to continue attending the scheduled study visits through the Week 48 Visit even if the participant discontinues study drug. Participants on Treatment 2 (SBR) who discontinue their baseline regimen due to an AE prior to Week 24 will be asked to continue attending the scheduled study visits through the Week 24 visit.

h HIV TSQs is to be completed at Day 1. The HIV TSQc is to be completed at Week 4 and Week 24. Participant is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires.
i VAS Adherence Questionnaire will be administered at Day 1 and at all visits up to (and including) Week 24 for participants in Treatment Group 2 (SBR) only.
j Complete physical exam is required at Screening, Day 1, Week 24, 48, 72, and ESDD. Urogenital/anorectal exams will be performed at the discretion of the Investigator. Symptom directed physical examination, as needed.
k Vital signs measurements including blood pressure, pulse, respiratory rate, and temperature.
l All female participants will have a serum test performed at Screening. Urine pregnancy test will only be done for persons of childbearing potential. Positive urine pregnancy tests will be confirmed with a serum test.
m FSH test is required for female participants who are <54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.
n Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, amylase, and Cystatin C. After Day 1, calcium, phosphorous, magnesium, and amylase (reflex lipase testing is performed in participants with total amylase > 1.5 x ULN) will not be collected. Analyses of glucose will be done as part of the fasting metabolic assessments, and not as part of the chemistry profile at Day 1, Weeks 24, 48, and 72. Cystatin C will only be collected at Day 1.
o Metabolic Assessments will be performed at Day 1, Weeks 24, 48, and 72. Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
p CBC with differential and platelet count.
q HIV 1 genotype and phenotype testing for participants with confirmed virologic failure and HIV 1 RNA >200 copies/mL. Following virologic rebound, participants will be asked to return to the clinic (2 3 weeks later) prior to the next scheduled visit or at the next scheduled study visit for a HIV 1 RNA and HIV 1 resistance analysis (reverse transcriptase, protease, and integrase genotype and phenotype) blood draw. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema.
r [redacted]
s HBV blood panel will be performed at Screening and Week 48: HBsAg, HBsAb, HBcAb.
t **For participants who are HBV co-infected (defined in Protocol Section 6.9.1):** The following HBV Blood panel will be conducted by the central laboratory: HBsAb, HBsAg (qualitative and quantitative), and HBeAg (if negative, reflex HBeAb).
For participants who are NOT HBV co-infected: The following HBV Blood panel will be conducted by the central laboratory: HBsAb, HBcAb, and HBsAg. Participants who are HBsAg or HBcAb positive will have a reflex test for HBV DNA (viral load).
u **For participants who are HBV co-infected:** Plasma HBV DNA will be collected at Day 1, Week 24, Week 48 and ESDD.
v Hepatitis C virus serology will be performed at Screening, Week 48, and Week 72. Participants who are HCVAb positive will have an HCV RNA test performed.
w Plasma, serum, and urine storage samples will be collected for safety, virology, or PK testing.
x Collect whole blood sample for participants randomized to SBR only at Week 24.
y [redacted]
z Randomization may be performed up to 3 days prior to the in clinic Day 1 visit provided that all screening procedures have been completed and participant eligibility has been confirmed.
aa At Week 24, participants randomized to continue their baseline regimen and complete 24 weeks of treatment on their baseline regimen will switch to FDC of B/F/TAF.
bb FDC of B/F/TAF will be dispensed to Treatment Group 1 only. Study drug accountability will be performed accordingly.
cc Participants will receive study drug for dosing until Week 72.

Appendix 2. Flowchart of US FDA-defined Snapshot Algorithm (for Switch Trial)

The following flowchart for US FDA-defined snapshot algorithm is based on the US FDA Guidance on Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for treatment {U. S. Department of Health and Human Services 2015}.



* On-Treatment HIV-1 RNA data include all HIV-1 RNA data for subjects who are on-going and HIV-1 RNA data up to 1 day after the last dose date of study drug for subjects who prematurely discontinue or complete study drug.

Appendix 3. Cardiovascular or Cerebrovascular Events

An adverse event record will be flagged as a cardiovascular or cerebrovascular event if its MedDRA PT is included in the pre-specified PT list, which includes all PTs from the narrow search of the following 3 SMQs under MedDRA v23.0 provided by Gilead GLPS (search name: Ischemic cardiac and cerebral events narrow) and reviewed by Gilead medical monitors.

	SMQ Source
Cardiovascular or Cerebrovascular Events	Ischaemic central nervous system vascular conditions (SMQ) – Narrow Scope Term
	Myocardial infarction (SMQ) - Narrow Scope Term
	Other ischaemic heart disease (SMQ) - Narrow Scope Term

Appendix 4. Hepatic Events

An adverse event record will be flagged as a hepatic event if its MedDRA PT is included in this pre-specified PT list, which includes all PTs from the broad search of the following 15 SMQs under MedDRA v23.0 provided by Gilead GLPS (search name: Non-infectious, non-congenital hepatobiliary disorders) and reviewed by Gilead medical monitors.

	SMQ Source
Hepatic Events (HEP)	Biliary neoplasms benign (incl cysts and polyps) (SMQ)
	Biliary malignant tumours (SMQ)
	Biliary tumours of unspecified malignancy (SMQ)
	Biliary system related investigations, signs and symptoms (SMQ)
	Biliary tract disorders (SMQ)
	Gallbladder related disorders (SMQ)
	Gallstone related disorders (SMQ)
	Cholestasis and jaundice of hepatic origin (SMQ)
	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)
	Hepatitis, non-infectious (SMQ)
	Liver neoplasms, benign (incl cysts and polyps) (SMQ)
	Liver malignant tumours (SMQ)
	Liver tumours of unspecified malignancy (SMQ)
	Liver related investigations, signs and symptoms (SMQ)
	Liver-related coagulation and bleeding disturbances (SMQ)

Appendix 5. Determining Missing and Virtual visits due to COVID-19

This appendix describes the site collection of COVID-19 data as pertains to missed/virtual visits and the data processing algorithm used to determine which visits were missing and which visits were virtual.

Data collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by data management to instruct clinical trial sites with respect to data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites should enter "Visit missed due to COVID-19." If a visit which was to be conducted in-person was conducted virtually, sites should enter "Virtual visit due to COVID-19."

Determination of Missed and Virtual visits

Natural Language Processing (NLP) was used to search the CRF comment fields to identify instances of "COVID-19" (or synonyms, see Table X 1) and "Virtual" (or synonyms, see Table X 1). The search terms are maintained in a global lookup and can be modified and/or corrected to tune the NLP model. For each comment field the following algorithm was applied:

STEP 1: Eliminate extraneous text from each comment field, e.g. "and", "or", "for", etc. This is done using the list of extraneous terms given in Table X 2.

STEP 2: Check each of the remaining comment text strings against the "COVID-19" terms and "Virtual" terms with the Levenshtein distance, using SAS function COMPGED (Computes a generalized edit distance using the Levenshtein operations to compute/summarize the degree of difference between two text strings):

i. If Levenshtein distance < 149 for any of the "COVID-19" terms then COVIDFL 1, else COVIDFL 0

ii. If Levenshtein distance < 149 for any of the "Virtual" terms then VIRTFL 1, else VIRTFL 0

STEP 3: For any comments with COVIDFL 1, assign "Missed visit" or "Virtual visit as follows

i. IF COVIDFL 1 and the visit date is missing then result is 'Missed Visit'

ii. IF COVIDFL 1 and VIRTFL 1 then result is 'Virtual Visit'

iii. Otherwise result is missing

Table X 1. Examples of search terms for "COVID-19" and "Virtual" used to identify missed and virtual visits.

Search terms for "COVID-19"	Search terms for "Virtual"
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	TELEMEDICINE
LOCKDOWN	TELECONSULTATION
QUARANTINE	TELEPHONICALLY
SHELTER	PHONE
	HOME VISIT
	ZOOM
	SKYPE

Table X 2. Examples of extraneous text terms to eliminate from the comment fields.

a	down	in	she'd	until
about	during	into	she'll	up
above	each	is	she's	very
after	few	it	should	was
again	for	its	so	we
against	from	it's	some	we'd
all	further	itself	such	we'll
am	had	i've	than	were
an	has	let's	that	we're
and	have	me	that's	we've
any	having	more	the	what
are	he	most	their	what's
as	he'd	my	theirs	when
at	he'll	myself	them	when's
be	her	nor	themselves	where
because	here	of	then	where's
been	here's	on	there	which
before	hers	once	there's	while
being	herself	only	these	who
below	he's	or	they	whom
between	him	other	they'd	who's
both	himself	ought	they'll	why
but	his	our	they're	why's
by	how	ours	they've	with
could	how's	ourselves	this	would
did	i	out	those	you
do	i'd	over	through	you'd
does	if	own	to	you'll
doing	i'll	same	too	your
down	i'm	she	under	you're
	you've	yourself	yourselves	yours

Appendix 6. Programming Specifications

1) If the age from the Day 1 eCRF is not available, age will be calculated as follows:

   Only year is provided for the date of birth (DOB). Use July 1 for the month and day.

   AGE (years) is calculated from the number of days between the DOB and Study Day 1,

   Use the SAS INTCK function to determine the number of "1st-of-month days" (eg, January 1st, February 1st, March 1st) between DOB and Day 1 (inclusive),

   Divide the result in (b) by 12,

   AGE the integer of the result in (c),

   Age for laboratory test reference range will be based on the age at the sample collection date.

2) All screened participants refer to all participants who are screened (ie, with non-missing screening date) and have a screening number. For summaries the same participant is counted only once. DOB and other demographic information such as sex, race, and ethnicity will be used to identify unique screened participants.

3) Screen failure participants are the participants who were screened and answered "No" for any inclusion criteria or "Yes" for any exclusion criteria regardless of which version of protocol the participant was consent to.

4) Participants in the randomized analysis set are defined as participants randomized into the study. IXRSRAND is the source to determine whether the participant is randomized (ie, participant with non-missing RGMNDTN in the IXRSRAND dataset), and confirmed by the eCRF ENROLL dataset (ie, ENROLLYN "Yes" in ENROLL dataset).

5) Randomized treatment (ie, TRT01P in ADSL) is derived from IXRSRAND, while actual treatment received (ie, TRT01A in ADSL) is assigned as the randomized treatment if participant took at least 1 dose of study drug and assigned as blank if the participant was never dosed.

6) In disposition table, the reasons for premature discontinuation are displayed in the order as they appear on the eCRF.

7) Body mass index (BMI) and Body Surface Area (BSA)

   BMI and BSA will be calculated only at baseline as follows:

   - BMI (weight [kg]) / (height [meters]2)
   - BSA (m^2) SQRT([Height(cm) × Weight(kg)] / 3600)

   Baseline height and weight will be used for this calculation.

8) Please note, “Not Permitted”, “Unknown”, or missing categories will be excluded from percentage calculation. Except for Mode of infection (HIV Risk Factors), where “Unknown” will be included for percentage calculation, since a participant may fit more than 1 HIV risk factors, therefore percentage may add to more than 100% and no p-value will be generated.

9) Defining Baseline ARV Medication

   Baseline ARV Medication

   All participants are expected to enter the study on an ARV regimen other than FDC of B/F/TAF that consists of any two NRTIs + allowed 3rd agent for ≥ 6 months (see Protocol Section 4.2 for allowed agents)

   Using the ARV raw dataset, for the B/F/TAF treatment group, include all prior and/or current ARVs (ARV.INGRED where ARV.CMSCAT ”Prior ARV” or “Current ARV”), taken on or up to 4 days prior to first dose date as defined in Section 3.8.1 (or randomization date if not treated). For the SBR treatment group, include all prior and/or current ARVs (ARV.INGRED where ARV.CMSCAT ”Prior ARV” or “Current ARV”) taken on Study Day 1.

   Use the following rules to determine if the ARV medication is taken on Day 1:

- If ARV end date is before B/F/TAF first dose date -4 for B/F/TAF participants or Day 1 date for SBR participants then exclude. If “Ongoing” is not marked and the end date is completely missing, then exclude. See below for imputation rules for any partial dates of uncertainty.

- If ARV start date is after B/F/TAF first dose date for B/F/TAF participants (or Day 1 visit date for SBR participants) then exclude. See below for imputation rules for any partial dates of uncertainty.

  The different categories used for the baseline ARV medication are (1) backbone, (2) third agent, and (3) third agent class.

- For participants with more than one baseline ARV medication record, concatenate the records together using “+” to get one record for each participant. For all ingredients, replace “_” or “+” with “/”.

- For each participant, search for the NRTIs: FTC, TAD, TDF, ABC, AZT, and 3TC. There should be 2 NRTIs for each participant. Create the backbone variable by concatenating the 2 NRTIs listed in the order above and separate by a “/” as per the backbone column in the table below.

- For each participant, identify the Third Agent. These will fall into 4 categories (PI, NNRTI, INSTI, and CCR5 antagonist). Each participant should have only 1 category of third agent unless they have a protocol deviation. For each participant, create the third agent variable by selecting on the ingredients listed:

  PIs and boosted PIs include ATV, ATV/RTV, ATV/COBI, DRV/RTV, DRV/COBI, LPV/RTV, and NFV. Create the third agent variable by concatenating the ingredients (ATV, DRV, LPV, NFV, RTV, COBI) with a "/". Change "ATV/RTV" to "ATV/r", "ATV/COBI" to "ATV/co", "DRV/RTV" to "DRV/r", "DRV/COBI" to "DRV/co", and "LPV/RTV" to "LPV/r", as per the Third Agent column in the table below.

  NNRTIs include DOR, EFV, NVP, and RPV. ETR is not allowed but is to be included for participants who were not on a protocol-approved baseline ARV medication.

  INSTIs include DTG, EVG/COBI, and RAL. Create the third agent variable by concatenating the ingredients (DTG, EVG, COBI, RAL). Change "EVG/COBI" to "EVG/co" as per the Third Agent column in the table below. RAL/RTV is a protocol violation and should be changed to "RAL/r".

  CCR5 antagonists include MVC.

  Each participant should have PI or NNRTI or INSTI or CCR5. If a participant has more than one, then it is a protocol violation. The third agent can be listed as "DTG/RPV" and should be counted in both categories for summary purposes.

  The final Baseline ARV Medication will be presented as third agent + backbone as per the last column in the table below.

  The table below provides example records for each participant with the backbone, third agent, third agent class, and final baseline ARV Medication variables.

Baseline ARV Medications from the data	Backbone	Third Agent	Third Agent Class	Baseline ARV Medication
ABC/NVP/FTC/TAF*	ABC/FTC/TAF	NVP	NNRTI	NVP+ABC/FTC/TAF
ATV/ABC/3TC	ABC/3TC	ATV	PI	ATV + ABC/3TC
ATV/RTV/ABC/3TC	ABC/3TC	ATV/r	PI	ATV/r + ABC/3TC
ATV/RTV/FTC/TAF	FTC/TAF	ATV/r	PI	ATV/r + FTC/TAF
ATV/RTV/FTC/TDF	FTC/TDF	ATV/r	PI	ATV/r + FTC/TDF
ATV/COBI/FTC/TAF	FTC/TAF	ATV/co	PI	ATV/co + FTC/TAF
DOR/FTC/TDF	FTC/TDF	DOR	NNRTI	DOR + FTC/TDF
DRV/COBI/ABC/3TC	ABC/3TC	DRV/co	PI	DRV + ABC/3TC
DRV/COBI/FTC/TAF	FTC/TAF	DRV/co	PI	DRV/co + FTC/TAF
DRV/COBI/FTC/TDF	FTC/TDF	DRV/co	PI	DRV/co + FTC/TDF

Baseline ARV Medications from the data	Backbone	Third Agent	Third Agent Class	Baseline ARV Medication
DRV/DTG/RTV/FTC/TAF*	FTC/TAF	DRV/r and DTG	DRV/r is PI DTG is INSTI	DRV/r and DTG + FTC/TAF
DTG/ABC/3TC	ABC/3TC	DTG	INSTI	DTG + ABC/3TC
DTG/FTC/TAF	FTC/TAF	DTG	INSTI	DTG + FTC/TAF
DTG/FTC/TDF	FTC/TDF	DTG	INSTI	DTG + FTC/TDF
DTG/RPV*	-	DTG and RPV	DTG is INSTI RPV is NNRTI	DTG and RPV
EFV/3TC/TDF	TDF/3TC	EFV	NNRTI	EFV + TDF/3TC
EFV/ABC/3TC	ABC/3TC	EFV	NNRTI	EFV + ABC/3TC
EFV/AZT/3TC	AZT/3TC	EFV	NNRTI	EFV + AZT/3TC
EFV/FTC/TAF	FTC/TAF	EFV	NNRTI	EFV + FTC/TAF
EFV FTC/TDF	FTC/TDF	EFV	NNRTI	EFV + FTC/TDF
ETR/ABC/3TC*	ABC/3TC	ETR	NNRTI	ETR + ABC/3TC
EVG/COBI/FTC/TAF	FTC/TAF	EVG/co	INSTI	EVG/co + FTC/TAF
EVG/COBI/FTC/TDF	FTC/TDF	EVG/co	INSTI	EVG/co + FTC/TDF
FTC/RPV/TAF	FTC/TAF	RPV	NNRTI	RPV + FTC/TAF
FTC/RPV/TDF	FTC/TDF	RPV	NNRTI	RPV + FTC/TDF
LPV/RTV/FTC/TDF	FTC/TDF	LPV/RTV	PI	LPV/r + FTC/TDF
MVC/FTC/TDF	FTC/TDF	MVC	CCR5	MVC + FTC/TDF
NFV/FTC/TAF	FTC/TAF	NFV	PI	NFV + FTC/TAF
NVP/AZT/3TC	AZT/3TC	NVP	NNRTI	NVP + AZT/3TC
NVP/FTC/TDF	FTC/TDF	NVP	NNRTI	NVP + FTC/TDF
NVP/FTC/TAF	FTC/TAF	NVP	NNRTI	NVP + FTC/TAF
RAL/ABC/3TC	ABC/3TC	RAL	INSTI	RAL + ABC/3TC
RAL/FTC/TAF	FTC/TAF	RAL	INSTI	RAL + FTC/TAF
RAL/FTC/TDF	FTC/TDF	RAL	INSTI	RAL + FTC/TDF
RTV/DRV/ABC/3TC	ABC/3TC	DRV/r	PI	DRV/r + ABC/3TC
RTV/DRV/FTC/TAF	FTC/TAF	DRV/r	PI	DRV/r + FTC/TAF
RTV/DRV/FTC/TDF	FTC/TDF	DRV/r	PI	DRV/r + FTC/TDF
RTV/RAL*	-	RAL/r	INSTI	RAL/r
TAF/COBI/DRV/FTC	FTC/TAF	DRV/co	PI	DRV/co + FTC/TAF
TAF/DTG/FTC	FTC/TAF	DTG	INSTI	DTG + FTC/TAF

*Protocol Violation

Duration of Baseline ARV Medication

Duration of the baseline ARV medication (defined above) prior/ to the first dose date is defined as (End Date Start Date+1). Duration will be expressed in years so that duration in days will be divided by 365.25 days.

End date is defined as the first dose date -1 or randomization date if randomized but not dosed.

Start Date: The start date of the baseline ARV medication is the latest start date of all the individual baseline ARV medications selected above

Use the following rules to handle any incomplete start dates

- If only month and year are available, day will be first imputed as 15th, then imputed as the minimum of (the start date of the ARV, first dose date-1, the stop date of the same ARV)
- If only year is available, month and day will be first imputed as July 1st of the year, then imputed as the minimum of (the start date of the ARV, first dose date-1, the stop date of the same ARV)
- No imputation applied for date missing completely

Use the following rules to handle any incomplete stop dates

- If only month and year are available, day will be first imputed as 15th, then imputed as minimum of (the first dose date-1, the stop date of the ARV)
- If only year is available, month and day will be first imputed July 1st of the year, then imputed as minimum of (first dose date-1, the stop date of the ARV)
- No imputation applied for date missing completely

10) Efficacy analyses:

The 95% CI for percentage estimate of HIV-1 RNA < 50 copies/mL or > 50 copies/mL for each treatment is calculated based on the Clopper-Pearson exact method.

```
proc freq;
by trt;
tables event/ binomial;
exact binomial;
run;
```

Listing for US FDA-defined snapshot outcome:

In addition to flagging the values of HIV-1 RNA < 50 or ≥ 50 copies/mL for virologic outcomes, flag the last available HIV-1 RNA value while on treatment for the following categories:

HIV-1 RNA > 50 copies/mL - Discontinued Study Drug Due to AE or Death and Last Available HIV-1 RNA > 50 copies/mL

HIV-1 RNA > 50 copies/mL - Discontinued Study Drug Due to Other reason* and Last Available HIV-1 RNA > 50 copies/mL

No virologic Data Discontinued Study Drug Due to AE or Death and Last Available HIV-1 RNA < 50 copies/mL

No virologic Data Discontinued Study Drug Due to Other reason* and Last Available HIV-1 RNA < 50 copies/mL

Note:* Other reasons include participants who discontinued study drug due to investigator's discretion, subject decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

11) TEAE

Events with Missing Onset Day and/or Month

An event is considered treatment emergent if the following 3 criteria are met:

i. The month and year (or year) of onset date is the same as or after the month and year (or year) of the first dose of study drug, and

ii. The month and year (or year) of the onset date is the same as or before the month and year (or year) of the 30th day after the date of the last dose of study drug, and

iii. End date is as follows:

The (complete) end date is on or after the first dose date, or

The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of study drug, or

End date is completely missing

Events with Completely Missing Onset Date

An AE with a completely missing onset date is defined as TEAE if end date meets any of the criteria specified in 3) above.

12) Toxicity Grades:

For toxicity grade summaries, include post-baseline graded results as defined in Section 7.2.2.1, not just those used in by-visit summaries.

13) Graded Laboratory Abnormalities Summary

The following labels will be used for treatment-emergent laboratory abnormalities and treatment-emergent Grade 3 or 4 laboratory abnormalities summary tables and listings:

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
Hematology	Hemoglobin	Decrease	Hemoglobin (Decreased)
	Neutrophils	Decrease	Neutrophils (Decreased)
	Platelets	Decrease	Platelets (Decreased)
	WBC	Decrease	WBC (Decreased)
Chemistry	Albumin	Decrease	Albumin (Decreased)
	Alkaline Phosphatase	Increase	Alkaline Phosphatase (Increased)
	ALT	Increase	ALT (Increased)
	Amylase	Increase	Amylase (Increased)
	AST	Increase	AST (Increased)
	Bicarbonate	Decrease	Bicarbonate (Decreased)
	Corrected Calcium	Increase	Corrected Calcium (Hypercalcemia)
	Corrected Calcium	Decrease	Corrected Calcium (Hypocalcemia)
	Creatine Kinase (CK)	Increase	Creatine Kinase (Increased)
	Creatinine	Increase	Creatinine (Increased)
	Lipase	Increase	Lipase (Increased)
	Magnesium	Decrease	Magnesium (Hypomagnesemia)
	Phosphate	Decrease	Phosphate (Hypophosphatemia)
	Serum Glucose (Fasting)	Increase	Serum Glucose (Fasting, Hyperglycemia)
	Serum Glucose (Fasting)	Decrease	Serum Glucose (Fasting, Hypoglycemia)
	Serum Glucose (Nonfasting)	Increase	Serum Glucose (Nonfasting, Hyperglycemia)
	Serum Glucose (Nonfasting)	Decrease	Serum Glucose (Nonfasting, Hypoglycemia)
	Serum Potassium	Increase	Serum Potassium (Hyperkalemia)
	Serum Potassium	Decrease	Serum Potassium (Hypokalemia)
	Serum Sodium	Increase	Serum Sodium (Hypernatremia)
	Serum Sodium	Decrease	Serum Sodium (Hyponatremia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)
	Total Cholesterol (Fasting)	Increase	Total Cholesterol (Fasting, Hypercholesterolemia)
	Triglycerides (Fasting)	Increase	Triglycerides (Fasting, Increased)
	LDL (Fasting)	Increase	LDL (Fasting, Increased)
	Urea Nitrogen (BUN)	Increase	Urea Nitrogen (Increased)
Urinalysis	Urine Blood (Dipstick)	Increase	Urine RBC (Hematuria, Quantitative or Dipstick)*
	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine RBC (Quantitative)	Increase	Urine RBC (Hematuria, Quantitative or Dipstick)*

Note: Prothrombin Intl. Normalized Ratio (INR) and Prothrombin Time (PT) were graded based on the protocol defined toxicity grade scale. The results and toxicity grade will be listed in listing, but not be summarized in lab toxicity summary table.

Due to the reflexive nature of the quantitative urine RBC test, results will be combined with the dipstick test of urine blood as described below. General rule is that urine RBC (Quantitative) should always be used first (if available), no matter if it is collected at the same time of Urine Blood (Dipstick) or not. The combined Urine RBC (hematuria, Quantitative or Dipstick) toxicity grade will be used for "Maximum treatment-emergent toxicity grade" summary.

Is Post-BL Urine RBC (Quant.) Result Available?	Is BL Urine RBC (Quant.) Result Available?	Is Post-BL Urine Blood (Dipstick) Result Available?	Is BL Urine Blood (Dipstick) Result Available?	How to Determine Treatment-Emergent Toxicity for " Urine RBC (Hematuria, Quantitative or Dipstick)"
Yes	Yes			Compare post BL Urine RBC (Quant.) toxicity grade to BL Urine RBC (Quant.) toxicity grade. If post BL toxicity is greater than BL toxicity, then treatment emergent
Yes	No			Treatment emergent. Use post BL Urine RBC (Quant.) toxicity grade.
No		Yes	Yes	Compare post BL Urine Blood (Dipstick) toxicity grade to BL Urine Blood (Dipstick) toxicity grade. If post BL toxicity is greater than BL toxicity, then treatment emergent
No		Yes	No	Treatment emergent. Use post BL Urine Blood (Dipstick) toxicity grade.
No		No		Do not count participant in the denominator for "Urine RBC (Hematuria, Quantitative or Dipstick)"

BL Baseline. Quant Quantitative. " " means any value can be present (or it can be missing), as it does not affect the classification

14) Concomitant nonstudy drug ARV medications (ie, ARV medications other than study drug that are taken while receiving study drug) will be flagged in "Nonstudy Drug Antiviral Medication" listing. The logic to define concomitant nonstudy drug ARV is similar to concomitant non-ARV Medications (see details in Section 7.4.2)

15) Lipid modifying medication analyses:

- Lipid modifying medication is defined to be the concomitant medication with WHO Drug ATC2 term (drug class) "LIPID MODIFYING AGENTS" and WHO Drug preferred drug name (CMDECOD) contains wording of "STATIN" in the ADCM dataset.

- Participants who took lipid modifying medications at baseline refer to the participants who have any use of the lipid modifying agents at Study Day 1.

    a) More specifically, participants with "Lipid Modifying Agent Use at Baseline" include those participants in the B/F/TAF safety analysis set meeting both of the following criteria: 1) any selected CM record with the start date ≤ the first dose date, and 2) the end date of the selected CM record ≥ the first dose date or the end date of the selected CM record is ongoing

b) For lipid modifying medications with the start date completely unknown, assume the start date is on or before the first dose date; lipid modifying medication is considered as being taken at baseline if the end date is not prior to the first dose date (ie, the end date is on or after the first dose date, completely unknown, or ongoing).

c) Lipid modifying medications with the start date prior to the first dose date and the end date unknown (completely missing) are considered as being taken at baseline (the unknown end date is assumed to be on or after the first dose date).

- Participants who initiated lipid modifying medications during the study are defined as the participants in the B/F/TAF safety analysis set who did not take lipid modifying medications at baseline and met the following criteria: any selected CM record with start date after the first B/F/TAF dose date and on and prior to the last B/F/TAF dose date.

16) For figures, if at a visit where n (sample size) for any treatment group < 5, data for that treatment group will not be displayed at that visit in the figure, but all data will be included in the corresponding table summary.

17) Vital signs and weight, height, BMI will be in the same listing.

18) HIV/HBV and HIV/HCV Coinfection:

- The following table presents the HBV and HCV tests with all possible values. Values that have an asterisk after them denote a "positive" (or "quantifiable" for HBV DNA and HCV RNA) result while all others denote a "negative" result.

Label	LBTESTCD	LBTEST	Possible Values
HBsAg	ATT1	Hep.B Surf.Ag Quant(70)CL	NUMERICAL VALUE or "<0.05" or ">124925.00" (IU/mL)
HBsAg	ATT2	Hep. B Surf. Ag Qual(70) CL	"Repeat reactive, confirmed"*, "Repeat Reactive Unconfirmed", "Non Reactive"
HBsAb	CNT353	anti Hep B Surface Ag2 Qual	"Positive"*, "Negative"
HBcAb	CNT68	Hepatitis B Core Total	"Positive"*, "Negative"
HBV DNA	GET1883	HBV DNA CAP/CTM 2.0 EDTA CL	"No HBV DNA detected", "<20 IU/mL HBV DNA detected", ">170000000"*, NUMERICAL VALUE (IU/mL)*
HBV DNA	GET1884	HBV DNA CAP/CTM 2.0Dil EDTA CL	NUMERICAL VALUE (IU/mL)*
HCVAb	CNT350	Hepatitis C Virus Antibody	"Positive"*, "Indeterminate", "Negative"
HCV RNA	GET1881	HCV RNA CAP/CTM 2.0EDTA CL	"No HCV RNA detected", "<15 IU/mL HCV RNA detected", NUMERICAL VALUE (IU/mL)*

Note: HBVDNA AMPLIPREPTAQMAN 2.0 DIL(GET1884) is for HBV DNA CAP/CTM 2.0 >170,000,000 IU/mL.
HBsAg(ATT1) test is conducted when HBsAg(ATT2) results "Repeat reactive, confirmed", "Repeat Reactive Unconfirmed".

- For baseline coinfection, when considering the different laboratory tests, take the latest, non-missing record on or prior to the first dose date for each test (eg, HBsAg, HBsAb, HBcAb, and HBV DNA)

  The baseline coinfection status will be one of the three values: Yes/No/Null

  The following tables provide combinations of HBV and HCV tests and the corresponding baseline coinfection status

HBsAg	HBsAb	HBcAb	HBV DNA	Coinfection Status
Positive				Y
Negative	Positive			N
	Negative	Positive	Quantifiable	Y
			Not Quantifiable	N
			Missing	Null
		Negative		N
		Missing	Quantifiable	Null
			Not Quantifiable	N
			Missing	Null
	Missing	Positive	Quantifiable	Null
			Not Quantifiable	N
			Missing	Null
		Negative		N
		Missing	Quantifiable	Null
			Not Quantifiable	N
			Missing	Null
Missing	Positive			Null
	Negative	Positive	Quantifiable	Y
			Not Quantifiable	Null
			Missing	Null
		Negative		Null
		Missing		Null
	Missing			Null

HCVAb	HCV RNA	Coinfection Status
Positive	Quantifiable	Y
	Not Quantifiable	N
	Missing	Null
Negative		N
Missing	Quantifiable	Null
	Not Quantifiable	N
	Missing	Null

" " means any value can be present, as it does not affect the classification

- For incident coinfection, all laboratory tests must share the same accession number and if any set of values meets the criteria, then the participant is considered to have incident coinfection

  The incident coinfection status will be one of two values: Yes/Null

  The following tables provide combinations of HBV and HCV tests that are considered "Y" for incident coinfection status (all others are considered Null)

HBsAg	HBsAb	HBcAb	HBV DNA	Coinfection Status
Positive				Y
Negative	Negative	Positive	Quantifiable	Y
Missing	Negative	Positive	Quantifiable	Y

HCVAb	HCV RNA	Coinfection Status
Positive*		Y
	Quantifiable	Y

* Participants with positive HCVAb postbaseline must also have negative or missing HCVAb at baseline in order to be considered as having incident HIV/HCV coinfection.
" " means any value can be present, as it does not affect the classification

19) HBV DNA test codes: If the result of the lab test code GET1883 (HBV DNA CAP/CTM 2.0-EDTA-CL) is listed as ">170000000", then a reflexive test code GET1884 (HBV DNA CAP/CTM 2.0Dil-EDTA-CL) should be performed and will share the same accession number as the original GET1883 test. In this instance, use the result from GET1884 instead of GET1883 when determining HBV DNA.

20) In this study, only 3rd generation LDL is collected.

21) For nonstudy drug ARV listing, ARVs which were dosed between the first dose date and the last dose date (inclusive) will be flagged (eg, ^). However, please note, if CM end date is completely missing and the medication is not marked "Ongoing" and the CRF indicates 'Prior ARV', the ARV will not be flagged.

22) Last Dose Date and Last Study Date

    a) Last Dose Date for participants who permanently discontinued study drug was defined in Section 3.8.1.

       If last dose date is missing (eg, only year of last dose date is known or completely missing due to lost to follow-up), the latest of the B/F/TAF study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, excluding the date of 30-day follow-up visit, will be used to impute the last dose date.

       If the last dose date is a partial date (ie, month and year of last dose are known), the latest of the dispensing dates of study drug bottles, study drug start dates and end dates, and the imputed last dose date [day imputed as 15] will be used as the final imputed last dose date. However, if the dispensing date's month is after the last dose date's month, a data query is needed.

If the participant died and the death date is complete (ie, not partial date) and before the imputed last dose date, the complete death date should be used as the imputed last dose date.

Last Study Date is the latest of the study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date, for participants who prematurely discontinued study or who completed study according to the Study Completion eCRF. If study drug start date or end date is partially missing (ie, only year and month are known), the day will be imputed as 15 for the purpose of this analysis.

If the participant died and the death date is complete (ie, not partial date) and before the imputed last study date, the complete death date should be used as the imputed last study date.

23) The precision in reporting numerical values should be as follows:

Raw measurements will be reported the same as the data captured electronically or on the CRF.

Standard deviation and standard error will be reported to one more significant decimal place than the raw measurement.

Mean, median, minimum, Q1, Q3, maximum, 95% CIs will be reported to the same number of decimal places of the raw measurements.

Exceptions may be considered; for example, if more than 4 significant digits are provided for the measurement.

24) Duration of HIV Diagnosis (years) is defined as the year from the First Dose Date/Study Day 1 Date minus the year of HIV diagnosis from Disease Under Study (HIV) CRF page.

25) Duration of HIV Treatment (Years) is defined as the year from the First Dose Date/Study Day1 Date minus the year first started HIV treatment from Disease Under Study (HIV) CRF page.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Project Team Leader eSigned	17-Nov-2020 00:48:44
PPD	Biostatistics eSigned	17-Nov-2020 21:06:18