HVTN 702 Open Statistical Analysis Plan for Safety, Trial Monitoring, and Vaccine Efficacy Analysis

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Protocol version 3.0 (Oct. 5, 2017)
SAP Version 1.4
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SAP Approval Signature Page

HVTN 702
A Pivotal Phase 2b/3 multi-site, randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of ALVAC-HIV (vCP2438) and Bivalent Subtype C gp120/MF59 in preventing HIV-1 infection in adults in South Africa

I have read this Statistical Analysis Plan and approve its contents.

_____ _____

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SAP Modification History

The version history of, and modifications to, this statistical analysis plan are described below.

Date: September 7, 2016
Protocol version: 1.0
SAP version: 1.0

Date: August 28, 2018
Protocol version: 3.0 (October 5, 2017)
SAP version: 1.1

Modifications:

1) Section 2: Changed maximum follow-up from 36 months to 42 months in accordance with Protocol Version 3.0.

2) Section 3: clarified that the Week 26 at-risk cohort is defined based on ELISA testing results for uninfected participants and based on PCR testing results (if available) for infected participants. In the event that the PCR testing result is not available at visit 6 (Week 26) for an infected participant, the mid-point between the last RNA-negative and first RNA-positive date will be used to determine whether the participant is in the Week 26 at-risk cohort. In the event that the PCR testing result is not available at any visit for an infected participant, e.g., during an interim analyses when some participants might be recently diagnosed as HIV-infection with no retrospective testings performed yet, the participant will be included in the cohort only if his/her latest negative ELISA test is from a visit at or after visit 6.

3) Section 4.1: Clarified that the date of diagnosis will be used as the primary event-date for time-to-event analyses related to VE and added text for the secondary analyses that use other definitions for the HIV event date.

4) Section 4.2: Added sensitivity analyses of VE using EPIT.

5) Section 8: Added a new section on the general approach to handling missing data.

6) Section 9: Updated Fisher's exact test to Barnard's test and deleted paragraph describing testing of AEs by body system.

7) Section 10.2: Updated the development of risk score according to HVTN 705 SAP.

8) Section 10.3.1: Clarified the text regarding the overall cumulative incidence estimation by combining separate sex-specific incidence estimates. Also clarified that cumulative incidence-based estimator is considered primary while the Cox HR estimator is secondary. Added details on the variance estimate of VE based on stratified cumulative incidence.

9) Section 10.3.2: Added secondary objective analyses of VE by other demographic variables.

10) Added additional references.

Date: March 12, 2019
Protocol version: 3.0 (October 10, 2017)
SAP version: 1.2

Modifications:

1) Section 3: clarified that the mid-point between the last RNA-negative and first RNA-positive date will be used only when the PCR testing result is needed but temporarily not available to determine a participant's Week 26 at-risk cohort status.

2) Section 3: clarified that the first analysis of VE(6.5-24) will only occur when there are at least 30 PP infections pooled over both treatment groups.

3) Section 10.3.1: clarified the duration of follow up time for stable variance estimates of the cumulative incidence.

4) Added Section 12 on Statistical Software.

Date: March 28, 2019
Protocol version: 3.0 (October 10, 2017)
SAP version: 1.2

Modifications:

1) Section 3, Week 26 At-Risk Cohort: moved the details on how HIV-1 negative status is defined to Section 4.1. Immunogenicity Cohort: added that immune response endpoints may also be evaluated at time points other than Week 26/Month 6.5.

2) Section 4: removed Month 6.5 from list of ELISA study visits, in accordance with Appendix F of protocol.

3) Section 6: clarified the timing of the final analysis if the trial does not proceed to Stage 2.

4) Section 7.2, Secondary Endpoint 3: added Month 18.5 to the list of immunogenicity assessments, in accordance with Appendix F of the protocol. Secondary Endpoint 7: clarified that viral sequences at the EPIT will be assessed.

5) Section 7.3, Exploratory Endpoint 1: clarified that VL and CD4+ values measured after ART initiation will be censored "at the time of ART initiation".

6) Section 10.2: stated that behavioral risk score is based on baseline variables.

7) Section 10.3.1: clarified that censoring time is based on the minimum of the time of last contact with HIV testing or the end of the Month 24 visit window.

8) Section 10.3.2: stated that the VE analysis taking into account number of founder viruses may be conducted.

9) Section 10.5: specified that the time origin is the date of the Week 26 immunogenicity visit and that the analysis of VE in the PP cohort will exclude participants who did not receive the first four planned immunizations within the specified visit windows.

10) Section 10.6: deleted text regarding net response rates as these will not be reported.

11) Section 10.7: clarified that correlates of risk will be studied through Month 36 only if Stage 2 occurs.

12) Section 11.4.2: added text describing summary of PrEP monitoring based on self-reported PrEP data.

13) Section 13: clarified statisticians are blinded or unblinded to study treatment.

Date: Sep. 10, 2019
Protocol version: 3.0 (October 10, 2017)
SAP version: 1.3

Modifications:

1) Section 2: clarified that participants will be followed for 'at least' 36 months if Stage 2 occurs in accordance with Version 3.0 of the protocol.

2) Section 3: clarified 'planned immunizations' in the definition of the Per-Protocol cohort (same clarification made in Section 10.5); deferred the sampling and analysis plan of the correlates and sieve analyses to a separate document; added text describing the analysis plan for duplicate enrollments.

3) Sections 7.1 and 9: added AESIs as a safety endpoint for analysis.

4) Section 7.3: removed "time of initiation of ART" as an endpoint because ART is expected to start immediately after HIV diagnosis for all participants in accordance with the updated HIV treatment guidelines. Also removed "longitudinal" as VL and CD4+ T cell count are assessed separately at two time points.

5) Section 10.3.1 Added text describing analyses assessing potential time-variation in VE on the additive-difference scale in cumulative incidence rates between the vaccine and placebo groups. Moved text from Section 10.4 to Section 10.3.1 on the analysis of instantaneous hazard ratio over time using the nonparametric kernel estimation method. Clarified sex-stratified VE analyses by Cox regression will only be done at the final analysis.

5) Section 10.3.2: added text describing potential supportive analysis of VE over time using the TMLE method.

6) Section 10.4: added text on the potential use of the TMLE method to assess durability of VE.

7) Section 10.11: replaced the longitudinal analysis of post-diagnosis VLs and CD4+ T cell counts by time-point specific analyses. Removed text on 'Time to ART Initiation".

8) Section 11.2: added text to account for the effect of the Month 18 boost vaccination in the monitoring. Clarified that sex-stratified VE analyses will only be done at the final analysis.

Date: Jan. 22, 2020
Protocol version: 3.0 (October 10, 2017)
SAP version: 1.4

Modifications:

Section 3: clarified the analysis plan for duplicate enrollments.

Section 4.1: clarified the definition of EPIT.

Section 10.3.1: changed to use the Nelson-Aalen method to estimate cumulative incidence rates over time for the vaccine and placebo groups to be consistent with the primary VE analysis.

Section 10.2: added a description of the primary behavioral risk score.

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1 Objectives of HVTN 702

HVTN 702 is a randomized, double-blind, placebo-controlled Phase 2b/3 preventative HIV vaccine trial, conducted among adults aged 18-35 in South Africa who are at risk for HIV infection. No more than approximately 35% and no less than approximately 30% males (ie, persons assigned male sex at birth) will be enrolled.

1.1 Primary Objectives

1. To evaluate the preventive vaccine efficacy (VE) of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 for the prevention of HIV infection in HIV-seronegative South African adults over 24 months from enrollment

2. To evaluate the safety and tolerability of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 in adults in South Africa

1.2 Secondary Objectives

1. To evaluate durability of vaccine efficacy from enrollment through 36 months if Stage 2 occurs

2. To evaluate vaccine efficacy from Month 6.5 (Week 26) through 24 months post enrollment

3. To evaluate the immunogenicity of the vaccine regimen

4. To evaluate immunogenicity and immune response biomarkers among vaccine recipients at Month 6.5 (week 26 visit) as correlates of risk of subsequent HIV acquisition between Month 6.5 and Month 24. If Stage 2 occurs, the scope of analysis will be expanded and will include additional immunogenicity timepoints

5. To evaluate VE by various demographic characteristics, including sex at birth

6. If significant positive evidence of vaccine efficacy from enrollment through 24 months is seen, to assess if and how vaccine efficacy depends on genotypic characteristics of HIV such as signature mutations

7. To evaluate and compare genomic sequences of viral isolates from HIV-1 infected vaccine and placebo recipients, and use sieve analysis methods to assess whether there is evidence of vaccine-induced immune pressure on the viral sequences

1.3 Exploratory Objectives

1. To evaluate vaccine effects (vaccine activity) on virologic and immunologic outcomes (eg, HIV-1 viral load (VL) and post diagnosis CD4+ T-cell count) among HIV-1 infected participants for 6 months post diagnosis, irrespective of ARV use
2. To further evaluate the immunogenicity of the vaccine regimen, additional immunogenicity assays may be performed, and assays may be performed on samples from other timepoints, based on the HVTN Laboratory Assay Algorithm.
3. To evaluate the role of host genetic factors in the immune response to the vaccine regimen and in vaccine effects on study endpoints
4. To understand changes in risk behavior and the potential for risk compensation for all study participants
5. To assess use of biomedical interventions and biological and behavioral factors in the study cohort and how they modify vaccine efficacy
6. To conduct analyses related to furthering the understanding of HIV, immunology, vaccines, and clinical trial conduct

2 Follow-Up Period

All participants will be followed for a minimum of 24 months and a maximum of 42 months post-enrollment– unless an interim boundary is reached. At the end of Stage 1– when the last participant reaches Month 24– a decision will be made as to whether to proceed to Stage 2. Conducting Stage 2 entails following participants to at least Month 36 (see Section 5). Participants who are diagnosed with HIV-1 infection during the study will be followed for approximately 6 months following infection diagnosis.

3 Study Populations

We define 8 study cohorts that are analyzed for addressing various study objectives. This terminology is used throughout the protocol and statistical analysis plan (SAP). More details on HIV-1 infection diagnosis are provided in Section 4.

1. **Safety Cohort**: Randomized participants who receive at least one study injection of vaccine or placebo.
2. **Modified Intent-to-Treat (MITT) Cohort**: Participants in the Safety Cohort who are HIV-1 negative on the date of first injection (Day 0).

3. **Week 26 At-Risk Cohort**: Participants in the MITT Cohort who are HIV-1 negative at or after the 2 weeks post fourth immunization visit (Week 26/Month 6.5 visit, visit 6).

4. **Per-Protocol (PP) Cohort**: Participants in the Week 26 At-Risk Cohort who receive all planned immunizations (without any study product administration error) at the first four immunization visits within specified visit windows.

5. **Full Immunization Cohort (FIC)**: Participants in the MITT Cohort who have an HIV-1 negative test result at the 2 weeks after the sixth immunization visit and who receive all planned immunizations within specified visit windows.

6. **Immunogenicity Cohort (IC)**: Participants in the Week 26 At-Risk Cohort who are selected for measurement of immune response endpoints at the primary immunogenicity timepoint (Week 26/Month 6.5) and possibly other time points.

7. **Month 6.5+ Infected Cohort**: Participants in the Week 26 At-Risk Cohort who are diagnosed with HIV-1 infection through Month 36.

8. **Month 6.5-Month 24 Infected Cohort**: Participants in the Week 26 At-Risk Cohort who are diagnosed with HIV-1 infection through Month 24.

9. **MITT Infected Cohort**: Participants in the MITT Cohort who are diagnosed with HIV-1 infection through Month 36.

10. **Month 0-Month 24 Infected Cohort**: Participants in the MITT Cohort who are diagnosed with HIV-1 infection through Month 24.

The MITT Cohort and the Safety Cohort are very similar but not identical to a full Intention-to-Treat Cohort (ie, all randomized participants); the Safety Cohort differs by excluding randomized volunteers who do not enroll; and the MITT Cohort is the subset of the Safety Cohort that also excludes randomized participants discovered later to be HIV-positive by Day 0. Because of blinding and the brief length of time between randomization and enrollment - typically no more than 4 working days - we expect almost all randomized volunteers to be in the Safety Cohort. Given that eligibility for the study requires recent evidence of being HIV-1 uninfected (within 30 days prior to enrollment), we expect almost all enrolled participants to also be in the MITT Cohort.

The primary analyses of safety objectives will be based on the Safety Cohort, whereas the primary analyses of the vaccine efficacy objectives, and the secondary analyses of viral sequence data, will be based on the MITT Cohort. Secondary analyses of the vaccine efficacy objectives will be based on the Week 26 At-Risk Cohort and the Per-Protocol Cohort, in addition to the MITT cohort, where the first analysis of VE(6.5-24) will take place only when there are at least 30 PP infections pooled over both treatment groups. Analyses of vaccine

immunogenicity and of immune correlates of risk will be based on participants in both the Immunogenicity and Week 26 At-Risk Cohorts, with additional supportive secondary analyses conducted based on the intersections of the Immunogenicity and, respectively, Per-Protocol or FIC Cohorts.

The safety analysis will be done according to the treatment received (as treated), where participants with AEs or SAEs will be counted as vaccinated if they received at least one injection. The efficacy and immunogenicity analysis will be done according to the treatment randomly assigned (as randomized).

Samples for immunogenicity testing will be collected at the immunogenicity time-points and frozen for all participants, but assays will only be performed for individuals in the Immunogenicity Cohort. Additional assays and sampling plans related to addressing Secondary Objectives 3 and 4 will be described in a separate document on correlates and sieve analyses.

In the unexpected event of a duplicate enrollment, the interim safety data will be reported for each enrollment, considering these as separate participants, while noting in the report that a duplicate enrollment occurred. All final analyses will only include unique participants. For duplicate enrollments, the data collected under each enrollment will be combined and the participant will be identified using the participant ID of the first enrollment. For 'as treated analyses, the treatments received across both enrollments will be considered when determining the treatment group. MITT analyses will use the treatment group assigned at randomization from the first enrollment. These doubly-enrolled participants are excluded from the PP cohort.

4 Diagnosis of HIV-1 Infections

The main vaccine efficacy endpoint is diagnosis of HIV-1 infection during the follow-up period; additional vaccine activity endpoints are assessed in study participants diagnosed with HIV-1 infection. The occurrence of HIV-1 infection will be detected through HIV-1 ELISA tests administered at study visits at Months 0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36 post-randomization (see protocol Appendix F). Participants found to have evidence for HIV-1 infection will have additional testing performed to confirm the diagnosis of HIV-1 infection.

The vaccine-induced immune responses may lead to false positive HIV-1 tests and difficulty in interpretation. Therefore the study utilizes a specialized diagnostic algorithm (see Section 10.3 of the protocol), and blinded Endpoint Adjudicator(s) or designee(s) who will review all data that support diagnoses of HIV-1 infection. Only HIV-1 infection cases confirmed by the Adjudicator(s) or designee(s) will be counted as HIV-1 infections in the analysis.

4.1 'Look-back' Procedure for HIV-Specific PCR Testing

For all subjects diagnosed with HIV-1 infection, the sample available at the nearest date before the diagnosis date will be tested using HIV-specific PCR. If it is positive, then the sample at the second nearest date before the diagnosis date will be tested using HIV-specific PCR. This procedure will be repeated until an HIV-specific PCR negative test result is obtained or until a test is done for a Day 0 sample. We define the 'earliest post-infection time-point' (EPIT) as the earliest date for which an HIV-specific PCR test is positive with no negative HIV-specific PCR tests at later time points. Full-genome sequences will be obtained at this time-point for the analysis of VE by HIV genotype. The EPIT will be used as the event-date for sensitivity analyses of VE addressing the primary and secondary objectives.

4.2 Date of Infection Diagnosis and Infection Status

All potential HIV-1 infections will be reviewed by a blinded, independent Endpoint Adjudicator(s) and/or designee(s) who will define the date of diagnosis based on his/her judgment of all of the available diagnostic data. This date is assigned based only on diagnostic testing results collected prospectively over time; it does not consider the results of HIV-specific PCR tests that may be performed on earlier samples that are tested later. The date of HIV-1 infection diagnosis will be used as the primary event-date for time-to-event analyses related to VE, and as the time origin for the analysis of post-infection endpoints, unless otherwise specified.

Secondary analyses may also utilize other event time definitions, including the mid-point between the left (L) and right (R) bounds of the true infection time with L and R chosen based on the actual set of diagnostic test results, taking into account knowledge of operating characteristics of the diagnostic tests, or infection time estimator that accounts for HIV diagnostics tests, viral loads through ART initiation and HIV-1 sequence diversity at post-infection time-points.

In the definition of various analysis cohorts; however, the results of HIV-specific PCR tests will be considered when available. Specifically, participants who are later determined to have been HIV-1 infected at enrollment based on HIV-specific PCR testing will be excluded from the MITT cohort; participants who are later determined to have been HIV-1 infected at Week 26 will be excluded from the Week 26 At-Risk Cohort; participants who are later determined to have been HIV-1 infected at Month 18.5 (visit 12) will be excluded from the Full Immunization Cohort; and participants who are later determined to have been HIV-1 infected at or before Month 24 (visit 14) will be included in the Month 6.5- Month 24 Infected Cohort, and the Month 0- Month 24 Infected Cohort. In the event that the PCR testing result is required to determine cohort status, but is temporarily not available for an infected participant at the relevant visit, the mid-point between the last RNA-negative and first RNA-positive date will be used to determine the cohort status. In the event that the PCR testing result is not available at any visit for an infected participant, e.g., during an

interim analyses when some participants might be recently diagnosed as HIV-infection with no retrospective testings performed yet, the participant will be consider HIV-1 negative at a given visit if his/her latest negative ELISA test is from a visit at or after the referred visit.

5 Stage 1 Analysis and Criterion for Continuing to Stage 2

Whereas the timing of interim analyses is event-driven, the total number of Stage 1 infections is not fixed. The end of Stage 1 is when the last enrolled participant reaches the Month 24 visit. Ensuring all participants are followed to Month 24 maximizes power and precision for assessing vaccine efficacy over Months 0-24 [VE(0-24)].

Early stopping of the vaccine regimen will be recommended if one of the potential harm or non-efficacy boundaries is met at a pre-specified analysis time, in which case a decision will be made regarding whether to follow participants to Month 24 (Stage 2 will not occur). If the high-efficacy boundary is met at a planned interim analysis, the vaccine regimen will be declared highly efficacious and placebo recipients may be offered the vaccine even while follow-up continues through Stage 1 (or Stage 2, if applicable). If none of the stopping boundaries are reached by the end of Stage 1, VE(0-24) is evaluated at the end of Stage 1.

If the lower bound of the 95% confidence interval for VE(0-24) is $> 0\%$ at the end of Stage 1 (equivalently, the 1-sided p-value for testing H0: VE(0-24) $\leq 0\%$ is above 0.025), trial participants will continue blinded follow-up through Stage 2. On the other hand, if at the Stage 1 efficacy analysis the lower bound of the 95% confidence interval for VE(0-24) $\leq 0\%$, Stage 2 will not occur even if none of the stopping boundaries were reached by the end of Stage 1. This corresponds to continuing to Stage 2 if, at the end of Stage 1, the estimated VE(0-24) is approximately 19-21% or greater; the range of VE values is due to uncertainty in the total number of Stage 1 infections.

6 Timing of Final Analysis

If the trial proceeds to Stage 2, the final analysis will occur when the last enrolled participant has reached the Month 36 visit, plus, if applicable, the additional number of weeks required such that the last HIV-1 infected participant reaches the final post-diagnosis (PD) visit. If the trial does not proceed to Stage 2, the final analysis will occur when the last enrolled participant has reached their final visit, plus the additional number of weeks required such that the last HIV-1 infected participant reaches their final post-diagnosis (PD) visit in Stage 1.

7 Endpoints

7.1 Primary Endpoints

For each study endpoint defined below, we include the cohort in which it is assessed.

Primary Endpoint 1 (MITT Cohort): Vaccine efficacy

HIV-1 infection diagnosed after enrollment (concurrent with first vaccination) through the Month 24 visit

Primary Endpoint 2 (Safety Cohort): Vaccine safety

Number and frequency of:

- Local reactogenicity signs and symptoms occurring within 3 days after each vaccine/placebo dose
- Systemic reactogenicity signs and symptoms occurring within 3 days after each vaccine/placebo dose
- Adverse events by body system, Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term, severity, and assessed relationship to study products within 30 days after each vaccine/placebo dose
- SAEs, AEs of special interest (AESIs), and new chronic medical conditions (defined as a new onset or exacerbation of medical condition requiring 2 or more visits to a medical provider during a period of at least 30 days) occurring at any time throughout the study
- AEs leading to early participant withdrawal or early discontinuation of study product(s) administration throughout the study

7.2 Secondary Endpoints

Secondary Endpoint 1 (MITT Cohort): Durability of VE

HIV-1 infection diagnosed after enrollment through 36 months post enrollment

Secondary Endpoint 2 (Week 26 At-Risk Cohort): Week 26+ VE

HIV-1 infection diagnosed after Month 6.5 through 24 months post enrollment

Secondary Endpoint 3 (Immunogenicity Cohort): Immunogenicity

Immune responses at Month 6.5 (Week 26 visit) from assays based on the HVTN Laboratory Assay Algorithm such as vaccine-specific binding antibodies and T cell responses. The primary time-point for immunogenicity assessment is the Week 26/Month 6.5 visit, 2 weeks after the Month 6 vaccination. Immunogenicity assessments will also be performed at the Month 0, 12.5, 18, 18.5, and 24 visits (the 'immunogenicity time-points' for measuring immune responses; see protocol Appendix F).

Secondary Endpoint 4 (Immunogenicity Cohort): Correlates of Risk

Immune responses from assays based on the HVTN Laboratory Assay Algorithm (available at https://atlas.scharp.org/) and/or more assays down-selected from a larger pool of pilot studies, in HIV-1-infected vaccine cases and HIV-1-uninfected vaccine controls.

Secondary Endpoint 5 (MITT Cohort): VE by demographics, including sex at birth

HIV-1 infection diagnosed after enrollment through Month 24, and through Month 36 if Stage 2 occurs, by demographic characteristics including sex at birth

Secondary Endpoint 6 (MITT Cohort): VE by HIV genotype

HIV-1 infection diagnosed after enrollment through Month 24, and through Month 36 if Stage 2 occurs, and genotypic characteristics of viral sequences from HIV-1-infected participants at first evidence of HIV-1 infection, such as signature site mutations.

Full genome HIV-1 sequences will be measured from each subject in the MITT Infected Cohort. Five sequences will be measured at the EPIT (earliest post-infection time-point, based on the 'look-back' procedure) and 5 sequences will be measured at a later visit selected to be between 3 and 6 months after the EPIT.

Secondary Endpoint 7 (MITT Infected Cohort): Sieve analysis

Viral sequences from HIV-1-infected participants at the EPIT

7.3 Exploratory Endpoints

This section lists endpoints for several key exploratory objectives.

Exploratory Endpoint 1 (MITT Infected Cohort): Vaccine effect on post-infection endpoints

Viral load (VL) at the time of HIV-1 infection diagnosis, and VL and CD4+ T cell count within 6 months PD

VL and CD4+ values measured after ART initiation will be censored at the time of ART initiation, because ART will typically have a strong effect on these biomarkers. VL values that are left- or right-censored by the quantification limits (40 to 10,000,000) of the primary

VL assay will be assigned value $\log_{10}(20)$, and right-censored values will be assigned a value $\log_{10}(10,000,000) = 7$.

Exploratory Endpoint 2 (Immunogenicity Cohort): Exploratory immunogenicity

Endpoints for additional immunogenicity assays performed on samples from immunogenicity timepoints, based on the HVTN Laboratory Assay Algorithm.

Exploratory Endpoint 3 (MITT Population): Host genetics

Host genetic factors including HLA alleles and KIR genes measured in the Immunogenicity Cohort

8 General Approach to Handling Missing Data

All primary analyses will assume missing data are missing completely at random (MCAR), i.e., that whether a data point is missing does not depend on any observed or unobserved data. When missingness is negligible, statistical methods based on the MCAR assumption can be used with limited impact on the analysis. We will assess the MCAR assumption in terms of whether subject characteristics are associated with time-to-event outcome (e.g., dropout) using the Cox regression model or with longitudinal binary outcome (e.g., missed visits) using logistic generalized estimating equation (GEE) models. When the frequency of missing data is more substantial, methods that require the MCAR assumption may give misleading results. In this situation, statistical analyses will be performed with methods such as targeted minimum loss-based estimation (TMLE) for cumulative incidence estimation, use of auxiliary covariates for the hazard ratio estimate (Lu and Tsiatis, 2008, Biometrika), covariate adjustment, weighting methods, or combined with imputation, under the assumption that the missing data are missing at random (MAR). MAR assumes that the probability of an observation being missing only depends on the observed responses or covariates. Thus, this assumption is less stringent than the MCAR assumption. We will consider including any of the available baseline predictors of the missing outcomes as covariates or auxiliary variables in statistical models.

9 Statistical Analysis of Safety

Safety endpoints will be assessed in the Safety Cohort. All analyses will only use samples and data gathered prior to study unblinding.

Reactogenicity The number and percentage of participants experiencing each type of reactogenicity sign or symptom will be tabulated by severity. For a given sign or symptom, each participant's reactogenicity will be counted once under the maximum severity for all injection visits. In addition to the individual signs or symptoms, the maximum severity of local

pain or tenderness, induration, or erythema, and of systemic symptoms will be calculated. Kruskal-Wallis tests will be used to test for differences in severity between the vaccine and placebo groups at the final analysis of reactogenicity.

Adverse experiences Adverse experiences (AE) will be analyzed using MedDRA preferred terms. The number and percentage of participants experiencing each specific adverse experience will be tabulated by severity and by relationship to treatment. For the calculations in these tables, each participant's adverse experience will be counted once under the maximum severity or the strongest recorded causal relationship to study product.

A listing of SAEs reported to the DAIDS Regulatory Support Center (RSC) Safety Office will provide details of the events including severity, relationship to study product, time between onset and last vaccination, and number of vaccinations received.

A listing of AESIs will provide details on severity, date of onset, relationship to study product, number of vaccinations received and days since last vaccination.

A listing of new chronic medical conditions (defined as a new onset or exacerbation of medical condition requiring 2 or more visits to a medical provider during a period of at least 30 days) occurring at any time throughout the study will be provided.

Reasons for discontinuation of vaccinations and early study termination The number (percentage) of participants who discontinue vaccinations and who terminate the study early will be tabulated by reason (including AEs leading to early participant withdrawal or early discontinuation of study product(s) administration throughout the study) and treatment arm.

Formal comparisons of reactogenicity and AE between treatment arms at final analysis To determine whether there are significantly different rates of safety endpoints between the vaccine and placebo groups, we will evaluate four aggregate endpoints based on the Barnard's exact test. These aggregate endpoints are the rate of any reactogenicity, the rate of any related adverse event, the rate of any reactogenicity of grade 3 or higher, and the rate of any related adverse event of grade 3 or higher.

See the Appendix for a complete list of the DSMB safety report tables and figures.

10 Statistical Analysis of Biological Efficacy, Activity and Clinical Endpoints

Except where specified, all vaccine activity and efficacy endpoints will be evaluated in the MITT cohort. All analyses will only use samples and data gathered prior to study unblinding.

10.1 Baseline comparability

Treatment groups will be compared with respect to baseline characteristics including demographics and laboratory measurements, using descriptive statistics (percentages, means, ranges).

10.2 HIV susceptibility risk score development

Several analyses will make use of a baseline behavioral risk score variable that will be developed. This section describes how this variable will be defined for each sex at birth.

We will use multivariable Cox proportional hazards modeling to develop a susceptibility risk score that is maximally predictive of the risk of HIV-1 infection during the trial. Based on the baseline behavioral risk assessment variables and baseline STI test results, in Step 1 we will define a set of candidate dichotomous risk factors, separately for each sex at birth. Non-dichotomous variables will be dichotomized as follows:

1. Sexual orientation: Heterosexual vs. non-heterosexual
2. Number of sex partners in the past month, dichotomized by dividing at the median
3. Condom use, general frequency: always vs. sometimes/never
4. Alcohol use and unprotected sex in past month: never vs. at least once
5. Spouse/main partner has other partners: yes/don't know vs. no
6. Parity: <3 vs. ≥ 3 live births
7. Circumcision status: circumcised vs. not circumcised/partially circumcised/exam not done

In Step 2, univariate Cox models will be fit for all of the dichotomous variables and treatment, pooling over the two treatment groups. Separate risk scores for the vaccine and placebo groups will also be developed, stratifying on treatment rather than pooling over it. All variables with an unadjusted score-test p-value $< .10$ will be screened-in for consideration in Step 3. In Step 3, all-subsets model selection will be used to select the optimal multivariate Cox model, again pooling over the treatment groups, using BIC as the criterion for the best model. Suppose that b variables are retained in the final best model, denoted by $X_1, \cdots, X_b$, where $X_j = 1$ indicates presence of the j^{th} risk factor. In Step 4, the baseline HIV susceptibility risk score for a subject is defined as

$$\text{risk score} = \frac{\sum_{j=1}^{b} w_j X_j}{\sum_{j=1}^{b} w_j}, \tag{1}$$

where w_j is the exponentiated regression coefficient (i.e., the adjusted relative risk associated with the risk factor) in the final multivariate model for variable j. This susceptibility risk score takes values between 0 and 1, with a greater risk score indicating a higher risk of HIV-1 infection.

Additional analyses may be conducted using a super-learning based risk score, described below, in place of the above risk score. Let Y denote the primary efficacy endpoint indicator (i.e., $Y = 1$ if the endpoint was observed and $Y = 0$ otherwise), W a vector of behavioral risk factors collected in a baseline questionnaire, and Z denote a vaccine indicator ($Z = 0, 1$ denotes placebo, vaccine). For the i^{th} participant, we define the baseline behavioral risk score as $\widehat{P}(Y_i = 1 \mid Z_i, W_i)$, where we use loss-based super-learning to estimate the best model for $P(Y = 1 \mid Z, W) = E_0[Y \mid Z, W]$ where E_0 denotes expectation under the true data generating distribution. This is a standard prediction problem. We estimate $E_0(Y \mid Z, W)$ with a minimizer of the risk of a loss: $\psi_0 = \arg\min_\psi P_0 L(\psi)$, with $Pf \equiv \int f(o) dP(o)$. We select binary log-likelihood loss $L(\psi)(O) = -\{Y \log \psi(W) + (1 - Y) \log(1 - \psi(W))\}$, given its good performance for a rare event outcome, and we stratify by Z when fitting the risk minimization problem to ensure that we are estimating $P(Y = 1 \mid Z, W)$ rather than $P(Y = 1 \mid W)$. To construct an optimal estimator among any given class of candidate estimators, we use loss-based super-learning. The oracle inequality for the cross-validation selector guarantees that the estimator is asymptotically at least as good as any candidate in the set of candidate estimators. We refer to (van der Laan et al., 2007) and (Rose and van der Laan, 2011) for details.

Let $\hat{\Psi}_j : \mathcal{M}_{NP} \to \Psi(\mathcal{M})$ be a candidate estimator that maps an empirical distribution of $(O_1, \ldots, O_n)$ (i.e., an element of the nonparametric model $\mathcal{M}_{NP}$ of probability distributions) into the parameter space $\Psi(\mathcal{M}) = \{\Psi(P) : P \in \mathcal{M}\}$, $j = 1, \ldots, J$. This library of candidate estimators could include a variety of parametric model based estimators as well as a variety of machine learning algorithms, possibly coupled with different dimension-reduction strategies, and possibly indexed by a variety of tuning parameters.

Let $B_n \in \{0, 1\}^n$ be a random split of the sample into a training sample $\{i : B_n(i) = 0\}$ and validation sample $\{i : B_n(i) = 1\}$. For example, if we use V-fold cross-validation defined by a partitioning of the sample in V equal size groups, then B_n has V possible realizations, each occurring with probability $1/V$, and each split corresponds with setting the components of B_n in one of the V-folds equal to 1 and setting the other components equal to 0. Let P^0_{n,B_n} and P^1_{n,B_n} be the empirical distributions of the training and validation sample corresponding with split-vector B_n, respectively. The cross-validated risk of the j-th candidate estimator is then defined as $E_{B_n} P^1_{n,B_n} L(\hat{\Psi}_j(P^0_{n,B_n}))$.

Define $\hat{\Psi}_\alpha = \sum_{j=1}^J \alpha_j \hat{\Psi}_j$ as a weighted linear combination of the candidate estimators, where the weights α_j are restricted to be non-negative and sum to 1. The cross-validation selector for the continuous family $\{\hat{\Psi}_\alpha : \alpha\}$ of candidate estimators is defined as:

$$\alpha_n = \arg\min_\alpha E_{B_n} P^1_{n,B_n} L(\hat{\Psi}_\alpha(P^0_{n,B_n})),$$

and the super-learner is then defined as $\hat{\Psi}(P_n) = \hat{\Psi}_{\alpha_n}(P_n)$.

By the oracle inequality for the cross-validation selector we have that, if the expectation of the loss-based dissimilarity $\min_\alpha E_{B_n} P_0\{L(\hat{\Psi}_\alpha(P^0_{n,B_n})) - L(\psi_0)\}$ between the oracle selected estimator and ψ_0 converges to zero at a slower rate than $1/n$, then

$$\frac{E_0 E_{B_n} P_0\{L(\hat{\Psi}_{\alpha_n}(P^0_{n,B_n})) - L(\psi_0)\}}{E_0 \min_\alpha E_{B_n} P_0\{L(\hat{\Psi}_\alpha(P^0_{n,B_n})) - L(\psi_0)\}} \to 1, \text{ as } n \to \infty.$$

In other words, excluding the unrealistic situation in which one of our candidate estimators is a correctly specified parametric model, the super-learner is asymptotically equivalent with the oracle selected estimator.

In addition, we can evaluate the super-learner by its cross-validated risk, using a cross-validation scheme S_n (e.g., using V-fold cross-validation again as in the super-learner):

$$\text{CV-RISK} = E_{S_n} P^1_{n,S_n} L(\hat{\Psi}(P^0_{n,S_n})),$$

which involves rerunning the super-learner on learning samples $\{i : S_n(i) = 0\}$ and evaluating it on test samples $\{i : S_n(i) = 1\}$, and averaging the performance across the different splits. When we do this for the trial, we will let S_n denote a random variable representing a mixture of 20 randomly selected 10-fold cross-validation schemes, so that the cross-validated risk can be evaluated by averaging the cross-validated risk from 20 different 10-fold cross-validation splits.

This represents an estimator of the true conditional risk

$$E_{S_n} R(\hat{\Psi}(P^0_{n,S_n}) \mid P_0) \equiv E_{S_n} P_0 L(\hat{\Psi}(P^0_{n,S_n})),$$

and one can also construct a Wald-type 95% confidence interval for the latter true conditional risk parameter $E_{S_n} R(\hat{\Psi}(P^0_{n,S_n}) \mid P_0)$ given by CV-RISK $\pm 1.96\sigma_n/\sqrt{n}$, where $\sigma_n^2 = E_{S_n} P^1_{n,S_n} \left\{ L(\hat{\Psi}(P^0_{n,S_n})) - E_{S_n} P^1_{n,S_n} L(\hat{\Psi}(P^0_{n,S_n})) \right\}^2$. The theory behind the asymptotic correctness of this data adaptive confidence interval is given in (Hubbard et al., 2016). We build the super-learner using the R package `SuperLearner` available on `CRAN`.

We will use super-learner with leave-one-out cross-validation, separately for the vaccine and placebo groups; leave-one-out is selected because it often performs well for small sample size data sets (with only 90–130 endpoint cases expected). Table 1 shows the input learners. We will plot point and 95% CI estimates of the cross-validated area-under-the-ROC curves (AUCs) (Hubbard et al., 2016) for each individual learning approach as well as for discrete super-learner and super-learner, and select the learner with the lowest cross-validated AUC for finalizing the 2 dimensional risk scores ($\widehat{P}(Y_i = 1 \mid Z = 0, W_i)$, $\widehat{P}(Y_i = 1 \mid Z = 1, W_i)$) defined as the estimated probability of HIV infection for the ith individual conditional on their baseline covariates, W_i, and treatment indicator. We will report the cross-validated AUC of the best model as a summary of the quality of the risk score.

Table 1: Learners used in the super-learner for building the baseline behavioral risk score for HVTN 702.

Learners	
Stepwise LR[a]	Best logistic regression model by AIC through a step-wise search
All Subsets	Best logistic regression model by AIC of all ≤ 5 variable combinations
GAM Step[b]	Best generalized additive model (GAM[d]) with 2 or 3 degrees of freedom, selected by AIC via step-wise search
Lasso[c]	
Regression tree[d]	
Random forest[e]	
Bayesian GLM[f]	

[a] The step-wise search begins with the full (all input variables) model. On the first step, it fits all remove-one-variable models and then removes one variable based on lowest AIC of the remove-one models. For next and subsequent steps, all models dropping or adding one variable are checked and a variable is dropped or added based on the model with lowest AIC. This procedure is repeated until no add-one-variable or drop-one-variable model has lower AIC than the current model.

[b] The generalized additive model step-wise search proceeds in similar manner as the step-wise logistic model search, beginning with the full model with no smoothing. Only the quantitative variables are considered for smoothing. On the first step, it fits all remove-one-variable models, all models with a single quantitative variable smoothed at 2 degrees of freedom and all models with a single quantitative variable smoothed at 3 degrees of freedom, and then selects the model based on lowest AIC. For next and subsequent steps, all models dropping or adding 1 variable and all models changing variables to 2 or 3 degrees of smoothing one at a time are checked and a variable is dropped, added, or changed based on the model with lowest AIC. This procedure is repeated until no add-one-variable, drop-one-variable, or change-one-variable model has lower AIC than the current model.

[c] Tibshirani (1996), regularization parameter selected via cross-validation

[d] Breiman et al. (1984)

[e] Breiman (2001)

[f] Gelman et al. (2008)

10.3 Primary Objective 1 (HIV-1 Infection Diagnosis)

10.3.1 Primary analysis of vaccine efficacy

The time between enrollment and the date of HIV-1 infection diagnosis will be evaluated in the MITT cohort. The failure times of subjects never observed to be diagnosed with HIV-1 infection will be right-censored at the date of last contact at which HIV testing was performed or the end of the Month 24 visit window, whichever occurs earlier.

Vaccine efficacy will be assessed using a ratio of cumulative incidences of HIV infection over the first 24 months (vaccine vs. placebo), estimated using the transformed Nelson-Aalen cumulative hazard function estimator, and tested using a Wald test. For the final analysis, the cumulative incidence estimation method will estimate incidence separately by sex and then combine the sex-specific incidence estimates into a VE estimate using the stratified Aalen-Johansen estimator with a single failure type (Aalen, 1978). The Nelson-Aalen estimator within a specific stratum is defined as $\widehat{H}_{\mathrm{NA}}(t) = \sum_{t_i \le t, \Delta_i = 1} d_i/n_i$, $t \ge t_{(1)}$ and its estimated variance as $\widehat{Var}(\widehat{H}_{\mathrm{NA}}(t)) = \sum_{t_i \le t, \Delta_i = 1} d_i/(n_i)^2$, $i = 1, \ldots, m$, where t_i indicates the i^{th} unique event time, d_i indicates the number of events at t_i, n_i indicates the number of individuals at risk shortly prior to t_i. The stratified cumulative hazard estimator is defined as $\hat{H}^s(t) = \sum_{k=1}^{K} w_k \hat{H}^k_{NA}(t)$ with $\sum w_k = 1$, where $\hat{H}^k_{NA}(t)$ indicates the Nelson-Aalen estimator based on the k^{th} stratum, and w_k the weight of the k^{th} stratum defined as the proportion of individuals in the stratum. To ensure the stability of the estimates, the cumulative incidence estimates are based on follow-up time until when there are at least 150 participants at-risk within each treatment group. Of note, interim analyses will not consider sex-stratified analyses. A sensitivity final analysis may be performed to estimate sex-pooled VE assuming a 50:50 sex ratio. Consequently, $\widehat{Var}(\hat{H}^s(t)) = \sum_{k=1}^{K} (w_k)^2 \widehat{Var}(\hat{H}^k_{NA}(t))$. The cumulative incidence is defined as $\mathrm{CI}(t) = 1 - \exp(-H(t))$, where $H(t)$, $t > 0$ denotes the cumulative hazard function at time t. CI(t) is estimated as $\widehat{\mathrm{CI}}(t) = 1 - \exp(-\widehat{H}^s(t))$ and its variance is approximated using the first-order Taylor expansion as $\mathrm{Var}(\widehat{\mathrm{CI}}(t)) = \mathrm{Var}(\exp(-\widehat{H}^s(t))) \approx [-\exp(-\widehat{H}^s(t))]^2 \mathrm{Var}(\widehat{H}^s(t))$. In addition, the variance of the log-transformed cumulative incidence ratio (vaccine vs. placebo), CIR(t), can be derived using first-order Taylor expansion approximation as $Var(\log(CIR(t))) = Var(\log(CI_{\mathrm{V}}(t))) + Var(\log(CI_{\mathrm{P}}(t))) \approx [1/CI_V(t)]^2 Var(CI_V(t)) + [1/CI_P(t)]^2 Var(CI_P(t))$, where $CI_V(t)$ and $CI_P(t)$ indicate the cumulative incidence estimate based on the vaccine and placebo groups, respectively.

Cox proportional hazards regression will also be used for estimating VE(0-24), measured by one minus the hazard ratio (vaccine vs. placebo), and for testing whether the VE(0-24) differs from 25%. For both interim and final VE analyses, both the cumulative incidence-based estimator and the hazard ratio estimator will be calculated but the former will be considered primary. Similar to the cumulative incidence-based analysis, for the final analysis, the Cox regression will stratify on sex at birth, allowing for a different baseline risk of HIV-1 infection by sex.

Note that the critical value for determining whether the vaccine effect on HIV-1 acquisition is significant at the two-sided 0.05 level will not require adjustment for the interim monitoring for vaccine potential harm or non-efficacy (see Section 11). This is because the monitoring that we use is designed to have minimal impact on the type-I error/power of the study. Moreover, whereas interim monitoring for vaccine efficacy would mean that the actual type-I error of the study is inflated above the nominal level, interim monitoring for non-efficacy or harm has the effect of decreasing the actual type-I error rate below the nominal level. In other words, use of the unadjusted critical value leads to conservative (as opposed to anti-conservative) inference, and again our simulations show that the degree of conservatism is minimal.

In addition, to assess potential time-effects of VE, the transformed Nelson-Aalen cumulative hazard function will be used to estimate cumulative incidence rates over time for the vaccine and placebo groups. This method will be used to estimate (i) cumulative vaccine efficacy over time, defined as (1 minus the ratio (vaccine/placebo) of cumulative incidence by time t) $\times$ 100%, and (ii) additive-difference vaccine efficacy over time, defined as the difference (placebo minus vaccine) in cumulative incidence by time t, with the method of Parzen, Wei, and Ying (1997) applied to obtain point-wise and simultaneous 95% CIs. To further explore potential time-variation in VE, instantaneous VE defined as one minus the instantaneous hazard ratio (vaccine/placebo) over time will be estimated using the nonparametric kernel estimation method with the asymptotic pointwise and simultaneous 95% CIs for instantaneous VE calculated following the method of Gilbert et al. (2002).

10.3.2 Supportive/sensitivity analyses of vaccine efficacy

Vaccine efficacy over time

As a supportive analysis of vaccine efficacy, targeted minimum loss-based estimation (TMLE) may be used to estimate cumulative incidences of the primary efficacy endpoint over time for the vaccine and placebo groups. Iterative mean-based TMLE is used for this analysis as described in Benkeser, Carone, and Gilbert (2016). The SuperLearner (van der Laan, Polley, and Hubbard, 2007) is used to generate initial estimates of the conditional censoring distribution and the iterated conditional means. The SuperLearner library includes both parametric and nonparametric algorithms: generalized linear models, generalized additive models with 2 or 3 degrees of freedom, a regression tree (Breiman et al., 1984), and a random forest (Breiman, 2001) (specified in Table 2). Each method considers adjustment for baseline demographic covariates, the baseline behavioral risk score built via supervised learning as described in Section 10.2, and two-way interactions of these terms. The candidate algorithms in the SuperLearner library considers various adjustments for time, as shown in Table 2. TMLE analysis will produce plots of estimated cumulative PE on both the multiplicative and additive-difference scales, as done for the primary analysis of VE. The TMLE analyses will be implemented using the R package `survtmle` available at CRAN. PE parameters may then be estimated as 1 minus the ratio (vaccine/placebo) of these TMLE estimators.

Table 2: Models included in the SuperLearner library. Z denotes vaccine/placebo assignment, B baseline behavioral risk score as described in Section 10.2, and W a vector of baseline demographic covariates. The columns indicate what type of candidate estimator was used (GLM = generalized linear model, step = stepwise GLM using both AIC and BIC as selection criteria, and GAM = generalized additive model), how time was modeled ($\emptyset$ denotes time was omitted from the model, `factor(t)` indicates dummy variables were used), and what covariates were included ($x * y$ indicates a cross product between covariates x and y). We use $s(x; df = d)$ to denote that variable x was modeled using a polynomial spline of degree d.

Model type	Time	Covariates
Conditional mean estimates		
GLM	$\emptyset$	Z
GLM	$\emptyset$	$Z + B + W$
GLM	$\emptyset$	$Z * B$
step	$\emptyset$	$Z * B + W$
Censoring estimates		
GLM	`factor(t)`	$\emptyset$
GLM	`factor(t)`	$Z * t$
GLM	$\emptyset$	Z
GLM	$\emptyset$	$Z + B + W$
GLM	t	Z
GLM	t	$Z + B + W$
GLM	$\log(t)$	Z
GLM	$\log(t)$	$Z + B + W$
step	`factor(t)`	$Z + B + W$
step	t	$Z + B + W$
step	$\log(t)$	$Z + B + W$
GAM	$s(t, 3)$	Z
GAM	$s(t, 3)$	$Z + B + W$
GAM	$s(t, 2)$	Z
GAM	$s(t, 2)$	$Z + B + W$

Influence-curve based variance estimators of each cumulative incidence is used, and the delta method applied to obtain the variance estimator of the log-cumulative incidence ratio. Point estimates and 95% pointwise and simultaneous Wald CIs for cumulative incidence curves and PE(t) curves will be plotted.

Vaccine efficacy by demographics including sex at birth

The primary VE analysis will be repeated by sex at birth, and possibly other demographics such as age (≤ 25 vs. > 25), body mass index, prevalent STI (ANY vs. NONE), and baseline

risk behavioral score. Generalized Wald tests for interaction will be used to test for evidence of differential VE by these demographics variables, using cumulative-incidence-based VE estimates. In the context of Cox proportional hazards models, Wald tests for interaction will be used to test for differential VE by demographics.

Vaccine efficacy absent PrEP

The primary analysis will be repeated, where only MITT infections subjects who were not using prophylactic ARVs at the time of HIV-1 diagnosis or first evidence of infection will be included in the analysis. Plasma drug levels will be used to determine eligibility for this analysis. A subject is eligible if the plasma drug levels are undetectable at the diagnosis visit and at the visit with earliest evidence of HIV-1 infection (if different from the diagnosis visit). Since the ARVs are only detectable in plasma for roughly 14 days (Patterson et al. 2010) and some subjects may have become infected before the 14-day window, with this approach we are not assured that all those included in the analysis were not using prophylactic ARVs at the time of infection. Therefore an additional analysis will address this issue by also excluding participants from the HIV-1 acquisition analysis if they self-reported drug use in the last 30 days at either the diagnosis visit or the last visit prior to diagnosis. This additional analysis will evaluate uninfected subjects without accounting for data on their plasma drug levels.

Vaccine efficacy, taking into account number of founding viruses

Another analysis may be conducted to assess VE(0-24) and VE(0-36) using the method of Follmann and Huang (2015) that incorporates information on the number of HIV-1 founder viruses in HIV-1infected participants. The method is expected to be more efficient than Cox proportional hazards regression if the vaccine reduces the number of founders.

10.4 Secondary Objective 1 (Durability of Vaccine Efficacy)

Vaccine efficacy over Month 0-36 [VE(0-36)] will be assessed using the method of Parzen, Wei, and Ying (1997) described above, as well as with nonparametric hazard ratio estimation (Gilbert et al. 2002) and with Cox proportional hazards modeling with time-dependent covariates. If the analysis suggests time-invariant vaccine efficacy, then Cox proportional hazards regression will be used to estimate and test VE(0-36).

Vaccine efficacy as a continuous function of time since entry [VE(t)] will be estimated using a variety of methods including the Cox model with flexible parametric regression coefficients and nonparametric smoothing (Gilbert et al. 2002). The TMLE method described in Section 10.3.2 may also be used. In addition, the causal inference method of Shepherd et al. (Shepherd et al. 2011; Shepherd et al. 2007) may be used to assess the causal vaccine efficacy over various time-periods in the subgroup that would be uninfected under either treatment assignment up to that time-point.

10.5 Secondary Objective 2 (Vaccine Efficacy, Months 6.5-24)

The primary vaccine efficacy analysis will be repeated in the Week 26 At-Risk Cohort, with the time origin the date of the Week 26 immunogenicity visit. Participants becoming HIV-1 infected or dropping out before Week 26 will be excluded from the analysis.

An analogous analysis will assess vaccine efficacy in the Per-Protocol Cohort. In addition to excluding participants becoming HIV-1 infected or dropping out prior to Week 26, this analysis will exclude participants who did not receive the first four planned immunizations (without any study product administration error) within specified visit windows.

In another analysis, the causal inference method of Gilbert, Shepherd, and Hudgens (2012) may be used to assess vaccine efficacy in the subgroup of participants who would be per-protocol under either treatment assignment.

10.6 Secondary Objective 3 (HIV-Specific Immune Responses)

Data from assays based on the HVTN Laboratory Algorithm will be summarized for each treatment group using geometric means and percentages of subjects with a positive response (using the standard HVTN method for calling a positive response). If assay data are qualitative (i.e., positive or negative) then analyses will be performed by tabulating the frequency of positive response for each assay by group at each time point that an assessment is performed. For the vaccine group, crude and net binomial response rates will be presented with their corresponding exact 95% confidence interval estimates. For the placebo group, the crude binomial response rate and exact 95% confidence interval estimates will be presented. These immunogenicity results will be used to demonstrate that the vaccine is immunogenic in the study population.

10.7 Secondary Objective 4 (Correlates of Risk)

Immune responses measured at Month 6.5 will be studied for their ability to predict HIV-1 infection through Month 24 and through Month 36, if Stage 2 occurs. Cox proportional hazards models that account for the case-control sampling design (Borgan et al. 2000) will be used for analysis. Selected analyses will be replicated using logistic regression models that take into account the sampling design (Breslow and Holubkov 1997).

10.8 Secondary Objective 5 (VE by Demographics)

The primary VE analysis will be repeated for subgroups defined by baseline subject characteristics. Generalized Wald tests for interaction will be used to test for evidence of differential

VE by subgroup, using cumulative-incidence-based VE estimates. In the context of Cox proportional hazards models, Wald tests for interaction will be used to test for differential VE by subgroup.

10.9 Secondary Objective 6 (VE by HIV Genotype)

A variety of methods including cause-specific Cox model and case-only method (Dai et al. 2014) may be used to assess genotypic characteristics of HIV as potential effect modifiers of VE(0-24) and VE(0-36).

10.10 Secondary Objective 7 (Sieve Analysis)

The sieve analysis will be conducted using updates of the methods that were used for the Step (Rolland et al., 2011) and RV144 HIV vaccine efficacy trials. The sieve analysis plan will be finalized before conducting the sieve analysis.

10.11 Exploratory Objective 1 (Post-Infection Endpoints)

VL at the diagnosis visit

To deal with the issue of missing VL data due to ART initiation and dropout PD, the robust-likelihood method of Little and An (2004) will be used to evaluate the vaccine effect on the VL at the diagnosis visit, with participants using prophylactic ARVs by plasma drug level and/or self report near the time of HIV-1 infection evaluated separately. A "complete case" analysis will also be performed, using a difference in sample average VL among subjects with observed VL values, with 95% confidence interval and p-value based on the standard t-statistic.

Post-diagnosis VLs and CD4+ T Cell Counts

Post-diagnosis VLs and CD4+ T cell counts will be analyzed at the Months 3 and 6 post-diagnosis time points based on data collected at each of these visits.

10.12 Exploratory Objective 2 (Additional Immunologic Endpoints)

The analysis of immunogenicity data will be repeated for the exploratory immunogenicity endpoints.

10.13 Exploratory Objective 3 (Host Genetics)

The HLA alleles of all subjects in the MITT Infected Population and in the Immunogenicity Subcohort will be measured. Additional host genetics, such as Fc-receptor genotypes, may be measured. These genotypes will be studied for their relation to immune responses at the primary Month 6.5 time point using regression modeling, where genotypes with putatively similar functionality will be grouped for analysis. If there is evidence of vaccine efficacy, VE(0-24) and VE(0-36) will be evaluated by host genotype, using these same groupings.

11 Monitoring of trial

HVTN 702 will be formally monitored for four types of events that may lead to a modification or termination of the trial. The first three monitor vaccine efficacy for potential-harm, non-efficacy/efficacy futility, and high-efficacy. Fourth, the DSMB will monitor the trial for operational futility, defined as overly slow enrollment, accrual of study endpoints, or other measures of under-performance (Section 11.3). Semi-annual DSMB meetings will be held, although not all will involve formal vaccine efficacy analyses. Of note, all four types of monitoring apply to pooled data across both sexes. Sex-specific infection numbers, incidence estimates, and VE estimates will be provided to the DSMB, but no formal sex-specific monitoring guideline will be used due to the smaller number of infections, and hence lower precision estimation, within each sex.

11.1 Monitoring for an Elevated Rate of HIV-1 Infection in the Vaccine Group

The unblinded statisticians (see Section 11) will continuously monitor the trial (i.e., examine the data after each confirmed MITT infection endpoint) for early evidence of a potential elevated rate of HIV-1 infection in the vaccine group compared to the placebo group. Such analyses start at the 12^{th} infection (pooled over treatment arms) and at each additional infection until the first interim analysis for non-efficacy, after which the non-efficacy analyses serve the function of potential harm monitoring. If the prespecified stopping boundary is reached, then the unblinded statisticians will immediately inform the DSMB. In addition, the DSMB chair will be updated on the accruing unblinded HIV-1 infection data after each confirmed MITT infection. This monitoring guideline is chosen to allow stopping for prudence as early as possible, maximizing participant safety. The monitoring is implemented with exact one-sided binomial tests of H0: $p \leq 0.5$ versus H1: $p > 0.5$, where p is the probability that an infected participant was assigned to the vaccine group. Each test is performed at approximately the same prespecified nominal/unadjusted alpha-level, chosen to control the overall type I error rate by the 59th arm-pooled infection (ie, the probability that the potential-harm boundary is reached when the vaccine is actually safe, $p = 0.5$) at

0.05. When a constant alpha does not exist that controls the overall type I error at the desired level, we use one that is as near as possible to constant. The impact on the potential harm monitoring is a very slight loss of power to detect a harmful vaccine.

The potential-harm monitoring is not intended to reliably establish harm [i.e., VE(0-24) $< 0\%$], as a vaccine regimen could meet the boundary and the reported 95% confidence interval for VE(0-24) would include 0% (although the 90% confidence interval, if constructed correspondent to the testing procedure, would exclude 0%). Rather, the objective is to apply extra caution and prudence for a prevention trial that enrolls healthy volunteers.

11.2 Monitoring for Vaccine Efficacy/Activity Futility

The DSMB will monitor the vaccine for non-efficacy/efficacy futility, defined as evidence that it is highly unlikely that the vaccine has a beneficial effect on acquisition of VE(0-24) or of VE(6.5-24) of 40% or more. Such analyses will start at 59 infections, which is chosen as the first infection total when a 95% confidence interval about an estimated VE(0-24) = 0% (based on a Cox proportional hazards model) would lie below 40%. The criterion for non-efficacy is that, for both VE(0-24) and VE(6.5-24), the lower limit of the 95% confidence interval lies below 0% and the upper limit lies below 40%. By checking both VE(0-24) and VE(6.5-24) confidence intervals, the monitoring plan is designed to protect against stopping prematurely based on ramping vaccine efficacy over the inter-current period of 0-6 months.

To account for the effect of the Month 18 boost vaccination (added in Version 3.0 of the protocol), it is recommended that non-efficacy/efficacy futility will only be declared if the above monitoring guidelines are met and at least 60% of total enrolled participants have reached the Month 18.5 visit. The DSMB will also be provided the following to aid decision-making in the monitoring of vaccine non-efficacy: 1) an estimate of VE(0-τ) where τ is the maximum follow up time when there are at least 150 participants at-risk within each treatment group, 2) for $\tau > 12$ months, an estimate of VE(12-min(τ, 30)) will also be provided, 3) for $\tau > 24$ months, instantaneous VE estimates over time until τ will also be provided, 4) for $\tau > 30$ months, an estimate of VE(0-30) will also be provided.

For each parameter, VE is estimated two ways. First, defining VE as one minus the ratio of cumulative HIV incidence estimates, vaccine vs. placebo, VE is estimated by the transformation of the Nelson-Aalen estimator for the cumulative hazard function. Second, VE measured by one minus the hazard ratio (HR) for HIV infection is estimated using Cox proportional hazards regression. Confidence intervals for both VE estimates must satisfy the non-efficacy criterion, for both VE(0-24) and VE(6.5-24). The rationale for using both cumulative-incidence-based and proportional-hazards-based VE estimates is that: 1) the former better protects against concluding non-efficacy due to ramping vaccine efficacy but the latter is more stable at early interim analyses; and 2) proportional-hazards-based VE estimates are used to determine when to start the interim monitoring and are universally used in vaccine efficacy studies.

11.2.1 Monitoring for high efficacy

Monitoring of high efficacy allows early detection of a highly protective vaccine if there is evidence that VE(0-36) $> 70\%$. Stage 1 high efficacy analyses will be harmonized with those for non-efficacy monitoring, with the exception that the high efficacy analyses will only start once at least 100 participants have reached the terminal Month 36 visit. This condition ensures that sufficient follow-up has accumulated to estimate VE(0-36). If Stage 2 occurs, there will also be one final high efficacy interim analysis at the midpoint of Stage 2, defined as 6 months after the end of Stage 1. The criterion for high efficacy is that the 95% confidence interval for VE(0-36) lies above 70%. Here again, VE is estimated using a ratio of cumulative incidences and using Cox proportional hazards regression, and the high efficacy criterion must be satisfied for both estimators. Note that, while the harm and non-efficacy monitoring restrict to infections diagnosed between Months 0 and 24, the monitoring for high-efficacy counts all infections during Months 0-36, given that early-stopping for high-efficacy would only be warranted under evidence for durability of the efficacy.

11.3 Monitoring for Operational Futility

The DSMB monitors the trial for operational futility, defined as overly slow progress toward full enrollment or insufficient numbers of MITT infections to support the primary analysis, and by other measures of under performance such as adherence and retention. Approximately semi-annual DSMB meetings will be held for monitoring operational futility during the closed session, synchronized with interim analyses of vaccine efficacy. At the DSMB meetings, projections will be made of the time until enrollment completes. Under design assumptions, enrollment is expected to take no more than 25 months, with a target of 20 months. The projection of this time will be presented to the DSMB and the OG, and compared with the pre-trial assumptions. The probability distribution of the projected treatment-arm-pooled infection total over 0-24 months will also be presented to the DSMB. The probability distribution of the Stage 1 (0-24 month) treatment-arm-pooled infection total, under design assumptions on enrollment, dropout, and infections, is shown in Table 3.

Table 3: Distribution of Stage 1 infections (pooled over treatment arms) ignoring interim monitoring

	Percentile				
True VE(0-24)	10%	25%	50%	75%	90%
0%	369	380	393	405	417
50%	277	286	297	308	319

In addition, projected probability of reaching two minimal needed treatment arm-pooled HIV-1 primary endpoint infection number targets, Target 1 and Target 2, by the end of Stage 1 in the MITT cohort will be presented. Projections based on both blinded (i.e.,

treatment arm-pooled) and unblinded (i.e., treatment arm-specific) data will be presented to the DSMB, whereas only the former will be presented to the OG. Enrollment modification or expansion may be considered if Target 1 cannot be met with some confidence. On the other hand, trial may be stopped early for operational futility to assess VE if Target 2 cannot be met with some confidence. Targets 1 & 2 are defined as follows and calculated by solving equation (1) in Schoenfeld (1983) using a null VE of 25% that assumes proportional hazards and ignores interim monitoring:

- Target 1 = 256: the total number of MITT HIV-1 infections needed to achieve 90% power to detect the trial design alternative VE(0–24) = 50% vs. $H_0 : \text{VE}(0\text{–}24) \leq 25\%$,
- Target 2 = 93: the total number of MITT HIV-1 infections needed to achieve 50% power to detect the trial design alternative VE(0–24) = 50% vs. $H_0 : \text{VE}(0\text{–}24) \leq 25\%$

In summary, the following information will be included in an operational futility report:

(a) the estimated distribution of the total (i.e., treatment arm-pooled) number of HIV-1 infections in the MITT cohort by the end of Stage 1, with corresponding power to reject $H_0 : \text{VE}(0\text{–}24) \leq 25\%$ using a 1-sided 0.025-level Wald test under the alternative hypothesis that VE(0–24) = 50%,

(b) the estimated probability that the total number of HIV-1 infections in the MITT cohort by the end of Stage 1 is ≥ 256 (Target 1) with 95% credible intervals,

(c) the estimated probability that the total number of HIV-1 infections in the MITT cohort by the end of Stage 1 is ≥ 93 (Target 2) with 95% credible intervals,

(d) the estimated distribution of the number of HIV-1 infections in the MITT cohort by the end of Stage 1 in each treatment arm,

The distributions in (a) and (d) will also be summarized by the mean number of HIV-1 infections with a Wald 95% confidence interval. The estimation procedures for (a)–(d) will be conducted under each of the following three scenarios:

(i) the treatment arm-pooled infection rates in (a)–(c), and the two treatment arm-specific infection rates in (d) used for generating future data are based on a Bayesian model and the prior assumptions that VE(0–24) = 50% (the design alternative) and the placebo incidence rate is constant over time,

(ii) the treatment arm-pooled infection rate in (a)–(c), and the two treatment arm-specific infection rates in (d) used for generating future data are based on a Bayesian model and the prior assumption that VE(0–24) = 25% (the null hypothesis), and

(iii) the treatment arm-pooled infection rate in (a)–(c) used for generating future data is based on a Bayesian model and the prior assumption that the infection rate equals the observed to-date infection rate.

The reason for conducting the estimation procedure under (i)–(iii) is that the purpose of the results in (b) is to trigger considerations about enrollment modifications, whereas the purpose of the results in (c) is to trigger considerations about early trial completion due to futility, where it is desired to reach a guideline based on (b) more easily/readily than a guideline based on (c). Accordingly, the results for (b) are interpreted focusing on the prior of VE(0–24) = 50% (i.e., scenario (i)), which makes it more likely to reach a guideline than the prior of VE(0–24) = 25%, and the results for (c) are interpreted focusing on the prior of VE(0–24) = 25% (i.e., scenario (ii)), which makes it less likely to reach a guideline than the prior of VE(0–24) = 50%. Results for (b) and (c) based on carrying forward the observed to-date infection rate in scenario (iii) provides additional guidance to the DSMB regarding considerations about enrollment modifications or early trial completion.

Furthermore, a treatment-blinded report will be generated for distribution to the OG at the time of each DSMB meeting and will report estimates listed in (a)–(c) above calculated based only on treatment-blinded data in scenarios (i-iii). The reported results pertaining to estimates (a)–(c) under scenarios (i-iii) will be identical to those in the DSMB report.

In addition, a special DSMB and OG report may be generated approximately 3 months before the projected completion of enrollment in order to provide timely information for a potential decision to modify enrollment before the enrollment apparatus is closed down. Under protocol assumptions, approximately 20% of the total person-years of Month 0-24 follow-up, and 66 Month 0-24 infections, will have accrued by the time the data will be cut for this report.

While it is the primary responsibility of the OG to make decisions regarding trial operations and modifications based on the monitoring of treatment-blinded primary endpoints, given the resource issues involved, DSMB review is also needed because issues of scientific integrity are also involved. More specifically, the DSMB can evaluate the progress toward primary endpoint targets in the context of the treatment-unblinded data, and based on this review may recommend to the OG to complete the trial early due to reaching a guideline for futility to assess VE (specified below).

The monitoring for futility to assess VE includes the following guidelines for trial modifications:

- **Guideline for enrollment modifications.** If, in the VE(0–24) = 50% scenario for the prior distribution in (i) using the robust prior defined in Section 11.3.2, the estimated probability of reaching 256 total infections in the MITT cohort by the end of Stage 1 is less than 25%, the OG may consider enrollment modifications with the intention to be able to conduct the primary VE analysis with sufficiently high power.
- **Guideline for futility.** If, in the VE(0–24) = 25% scenario for the prior distribution

in (ii) using the standard $\mathsf{Ga}(\alpha, \beta)$ prior as in Section 11.3.2, the estimated probability of reaching 93 total infections in the MITT cohort by the end of Stage 1 is less than 25%, the DSMB may recommend completing the trial early based on the inability to conduct the primary VE analysis with sufficiently high power. At the first operational futility analysis, a 20% probability threshold will be used rather than 25%, when there is very limited information about HIV incidence.

If enrollment is incomplete at the time of an interim futility analysis, then the outlined estimation procedures will use the average observed enrollment rate in approximately the last 6 months for generating future enrollment data. A Bayesian approach will be used for generating future HIV-1 incidence data, conditional on observed data to-date. More specifically, the estimates in (a)–(c) will condition on the observed to-date treatment arm-pooled HIV-1 incidence rate in the respective cohort, whereas the estimates in (d) will condition on the observed to-date treatment arm-specific HIV-1 incidence rates in the respective cohorts. All estimates in (a)–(d) will also use the observed to-date treatment arm-pooled dropout rate in the respective cohort for generating future dropout data. Further details of these calculations, including the prior distributions, are described in Section 11.3.1.

If, at any time, these guidelines for futility to assess VE are met and yet it appears that value exists in continuing the trial, the statisticians will provide the DSMB and the Leadership Group with additional information, as appropriate, for use in their consideration of whether to recommend early trial completion.

11.3.1 Estimation of the number of HIV-1 infection endpoints at an interim analysis

The method for estimating the probability distribution of the number of HIV-1 infection endpoints by the end of Stage 1 is based on the following approach to simulating this trial. The trial is modeled as a combination of three processes—enrollment, dropout, and HIV-1 infection—and a large number of trials is simulated. The three processes are assumed independent and their distributions are taken to be Poisson, exponential, and exponential, respectively. Data are generated at the level of the individual participant, such that, for each participant, we obtain an enrollment time, an (underlying true) infection time, and a dropout time. Only the minimum of the infection and dropout times is observable, and the average value for this minimum is beyond the duration of the trial, such that neither event will be observed for most participants.

In the absence of observed trial data, the treatment arm-pooled as well as the treatment arm-specific parameters for the infection and dropout processes are chosen to match our pre-trial assumptions about these rates. In addition, the infection rate considers both the design alternative of $VE = 50\%$ and the null hypothesis of $VE = 25\%$ in the calculation of the total and treatment arm-specific numbers of endpoints. More specifically, treatment arm-pooled calculations in (a)–(c) assume

- pooled infection rate [VE(0–24) = 50% scenario]: $0.5 \times 0.04 + 0.5 \times 0.5 \times 0.04 = 0.03$ infections/person-year at-risk (or 3% annual incidence rate),
- pooled infection rate [VE(0–24) = 25% scenario]: $0.5 \times 0.04 + 0.5 \times 0.75 \times 0.04 = 0.035$ infections/person-year at-risk (or 3.5% annual incidence rate).

We also assume a treatment arm-pooled dropout rate of 0.05 dropouts/person-year at-risk.

Treatment arm-specific calculations in (d) assume

- infection rate in the placebo arm: 0.04 infections/person-year at-risk,
- infection rate in the vaccine arm [VE(0–24) = 50% scenario]: $0.5 \times 0.04 = 0.02$ infections/person-year at-risk, and
- infection rate in the vaccine arm [VE(0–24) = 25% scenario]: $0.75 \times 0.04 = 0.03$ infections/person-year at-risk, and

In each arm, the dropout rate is assumed to be 0.05 dropouts/person-year at-risk.

The first step in simulating each trial is to enroll a certain number of participants per week according to a random draw from a Poisson distribution with rate parameter as listed above. Enrollment continues week-by-week until a total of 5,400 participants is reached. Second, each participant is assigned an exact enrollment day, uniformly distributed within their enrollment week. Following enrollment, the infection and dropout times are drawn from their respective exponential distributions, and the lesser of the two is recorded as occurring at the given time (possibly outside the time-window of the trial). We consider dropout events to have occurred at the dropout time (in days) that was generated (assuming it was less than the infection time). For participants who become HIV-1 infected, we record their time of diagnosis as the time of the first study visit following the true infection time. It is this time of diagnosis that we observe for infected participants.

A modification of the above procedure for simulating an efficacy trial is used for estimating metrics of futility to assess VE at a given interim analysis. The modification entails using the observed trial data to estimate parameters of the processes, rather than relying entirely on pre-trial assumptions. In particular:

- enrollment rate: if enrollment is incomplete, estimated based on the rate observed in approximately the last 6 months in the study,
- infection rate: drawn from a posterior distribution of the infection rate formed by combining the observed data with our prior specification about the infection rate based on the pre-trial assumptions, and
- dropout rate: estimated based on the treatment arm-pooled rate observed to date.

The rationale for a Bayesian approach for the infection rate (see Section 11.3.2 for details) is to help stabilize the infection rate early in the trial when insufficient time will have passed to accrue many infections. If we were to rely solely on the observed infections, we might by chance obtain very low rates, which would lead to an unrealistic prediction of the number of endpoints.

We consider various different gamma prior distributions for the infection rate in each of scenarios (i)–(iii) reflecting different weights assigned to the prior distribution (see Section 11.3.2 for details). Gamma distributions are considered because they are conjugate to the exponential distribution used for generating future infection data.

At a given interim analysis, 10^4 trials are simulated using the above procedure and treatment arm-pooled infection and dropout rates for estimates in (a)–(c). Separately, another set of 10^4 trials is simulated using the above procedure, treatment arm-specific infection rates, and the treatment arm-pooled dropout rate for estimates in (d). Each of these trials yields a projected number of infections by the end of Stage 1. These projected numbers of infections from each trial will be used to estimate the entire distribution of the number of infections by the end of Stage 1. The probability of reaching the target number of infections will be estimated as the proportion of trials with the projected number of infections greater than or equal to the target.

Figures on enrollment, HIV-1 incidence and dropout over time will also be included to aid interpretation of the results.

11.3.2 A Bayesian model for the HIV-1 incidence rate in estimation of the number of HIV-1 infection endpoints at an interim analysis

Let n_k and T_k denote, respectively, the infection count and the observed total person-time at risk at the time of the k-th futility analysis, pooling over all treatment arms. Additionally, let T^* denote the estimated total person-time at risk for the primary efficacy analysis at the end of Stage 1. Let the prior distribution of the pooled HIV-1 incidence rate p be $\mathsf{Ga}(\alpha, \beta)$ parametrized such that the prior mean $E\,p = \alpha/\beta$ (the same Bayesian method applies to the treatment arm-specific HIV-1 incidence rate). In scenario (i) for the treatment arm-pooled incidence rate, we additionally consider a robust prior distribution described in Section 11.3.2 used in the calculation evaluating the enrollment modifications guideline.

Generally, assuming that, conditional on p, the times to infection follow $\mathsf{Exp}(p)$, the posterior mean of p at the time of the k-th analysis equals

$$\begin{aligned} E[p \,|\, \text{data}] &= \frac{\alpha + n_k}{\beta + T_k} \\ &= \frac{\alpha}{\beta}\,\frac{\beta}{\beta + T_k} + \frac{n_k}{T_k}\,\frac{T_k}{\beta + T_k}, \end{aligned} \tag{2}$$

i.e., the posterior mean can be interpreted as a convex combination of the prior mean and the observed incidence rate. For a given $\beta > 0$, the weight on the prior mean at the first

analysis depends on the accumulated person-time at risk (T_1), and the weight will decrease in subsequent analyses because $\beta/(\beta+T_k)$ is a decreasing function of T_k, which is a desirable Bayesian property.

In order to identify α and β, it is desirable that the prior mean equals the pre-trial assumed treatment arm-pooled incidence rate p^* (e.g., under MITT VE(0–24)=50%, $p^* = 0.5\times 0.04 + 0.5 \times 0.5 \times 0.04 = 0.03$), i.e.,

$$\frac{\alpha}{\beta} = p^*. \tag{3}$$

Furthermore, we propose to consider three values of β that correspond to the weights $w = \frac{1}{2}$, $\frac{1}{4}$ and $\frac{1}{8}$ on the prior mean at the time when 50% of the estimated total person-time at risk has been accumulated, i.e., for each value of w, β is defined as the solution to the equation

$$\frac{\beta}{\beta + T^*/2} = w.$$

It follows that

$$\beta = \beta(w, T^*) = \frac{wT^*}{2(1-w)}\,, \tag{4}$$

and the estimation of T^* is described in Section 11.3.2. For $w = \frac{1}{2}$, $\frac{1}{4}$ and $\frac{1}{8}$, we obtain $\beta = \frac{T^*}{2}$, $\frac{T^*}{6}$, and $\frac{T^*}{14}$, respectively.

At the k-th futility analysis and for each of the three values of β, we will sample the treatment arm-pooled HIV-1 incidence rate from the posterior $\mathsf{Ga}(\alpha + n_k, \beta + T_k)$ for generating future data and report the weight $\frac{\beta}{\beta+T_k}$ on the prior mean in the convex combination (2).

A robust prior model for the HIV-1 incidence rate in the calculation evaluating the guideline for enrollment modifications The robust prior model (Schmidli et al., 2014) is implemented for the guideline to trigger enrollment modifications since it is designed to maximize the probability of meeting the guideline for large downward deviations from the protocol-assumed incidence rates, while minimizing a false trigger for protocol-assumed incidence rates.

The prior distribution of p is defined as a weighted mixture of two gamma distributions,

$$(1 - w_R)\mathsf{Ga}(\alpha_I, \beta_I) + w_R\mathsf{Ga}(\alpha_V, \beta_V),$$

where we set $w_R = 0.2$, and $\mathsf{Ga}(\alpha_V, \beta_V)$ and $\mathsf{Ga}(\alpha_I, \beta_I)$ represent the weakly informative and informative component of the mixture prior, respectively. The parameters β_V and β_I are calculated following (4) with $w = 1/1000$ and $w = 1/3$, respectively (and T^* per Section 11.3.2). Subsequently, α_V and α_I are calculated following (3) with p^* set to the pre-trial assumed treatment arm-pooled MITT incidence rate of 0.03 infections/person-year at risk.

The posterior distribution at the time of the k-th analysis is derived following the conjugacy principle, as in (2), which results in a mixture of conjugate posteriors with updated weights

$$(1-\widetilde{w}_{R,k})\mathsf{Ga}(\alpha_I+n_k,\beta_I+T_k)+\widetilde{w}_{R,k}\mathsf{Ga}(\alpha_V+n_k,\beta_V+T_k),$$

where

$$\widetilde{w}_{R,k}\propto w_{R,k}f_V/\left\{w_{R,k}f_V+(1-w_{R,k})f_I\right\}$$

with $f_\cdot$ equal to

$$f_\cdot=\frac{\Gamma(\alpha_\cdot+n_k)/(\beta_\cdot+T_k)^{\alpha_\cdot+n_k}}{\Gamma(\alpha_\cdot)/\beta_\cdot^{\alpha_\cdot}}$$

(see, e.g., Section 5.2.3, pages 279–282 in Bernardo and Smith (2000)).

Estimation of the total person-years at risk by the end of Stage 1 The total target sample size is $N=5400$, the duration of Stage 1 follow-up per participant is $\tau=2$ years, the pre-trial assumed dropout rate is $d^*=0.05$ dropouts per person-year at risk (PYR), and, in the MITT VE(0–24) = 50% scenario, the pre-trial assumed treatment arm-pooled HIV-1 incidence rate is $p^*=0.5\times0.04+0.5\times0.5\times0.04=0.03$ cases per PYR.

We consider the standard right-censored failure time analysis framework. Denoting the failure and censoring times as T and C, respectively, we assume that T is independent of C, $T\sim\mathsf{Exp}(p^*)$, and $C\sim\mathsf{Exp}(d^*)$. It follows that $X:=\min(T,C)\sim\mathsf{Exp}(p^*+d^*)$ and

$$\begin{aligned}
T^* &= N\times E[\min(X,\tau)]\\
&= N\times\left\{E[X\mid X\le\tau]\,P(X\le\tau)+\tau\,P(X>\tau)\right\}\\
&= N\times\left\{(p^*+d^*)\int_0^\tau x\exp^{-(p^*+d^*)x}\,\dot{\mathrm{x}}+\tau\exp^{-(p^*+d^*)\tau}\right\}\\
&= N\times\frac{1-\exp^{-(p^*+d^*)\tau}}{p^*+d^*}\,.
\end{aligned}$$

This results in $T^*=9980.29$ PYRs. For comparison, if all N participants were followed for τ years, the total PYRs would be $N\tau=10,800$ years.

Subsequently, for $T^*=9980.29$ PYRs, if $T_1=0.2\,T^*$, the weights $\frac{\beta}{\beta+T_1}$ on the prior mean at the first futility analysis in the MITT cohort corresponding to $w=\frac{1}{2}$, $\frac{1}{4}$, and $\frac{1}{8}$ are 0.71, 0.45, 0.26 respectively. If $T_1=0.3\,T^*$, the respective weights on the prior mean are 0.63, 0.36, and 0.19.

In addition, information on use of antiretroviral drugs that could affect accrual of endpoint infections will be provided to the DSMB as available. If the HIV incidence estimates are below projected despite good retention and adherence, the DSMB may elect to engage with the protocol team and oversight group as to what corrective actions can be undertaken, including expanding enrollment, and using specific demographic or behavioral risk factors to enroll higher risk participants or those coming from high epidemic communities.

If at any time these operational futility guidelines are met and yet it appears that value exists in continuing the trial, the statisticians will provide the DSMB with additional information, as appropriate, for use in their consideration of whether to recommend trial termination.

If the DSMB does recommend termination and the trial is stopped, then the final analysis will be performed and the results made public.

11.4 Pre-Exposure Prophylaxis (PrEP) Monitoring Plan

A non-ignorable level of PrEP use in the study population may impact the power of the study to assess vaccine efficacy by lowering the background HIV incidence. Although oral FTC/TDF as PrEP is currently not widely used in the HVTN 702 study population, prevalence of PrEP will be collected and monitored as a precaution. Specifically, measures of PrEP use will be reported by treatment arm to the DSMB, alongside other measures of study under-performance for assessing operational futility. In addition, both the study oversight group and the protocol team leadership will see treatment-arm-pooled estimates of PrEP use.

Dried blood spot (DBS) samples will be used to assess FTC/TDF use via an intracellular tenofovir diphosphate (TFV-DP) assay. Prevalence of FTC/TDF will be reported both as any detectable use and inferred effective use. Estimated percentages of person-years at-risk during any detectable FTC/TDF use and during inferred effective FTC/TDF use will be reported. The definition of effective use differs for men and women. Current knowledge about PrEP in MSM indicates consistent use of at least 4 doses a week is required to achieve substantial levels of protection. The lower quartile of simulated TFV-DP levels in DBS at 4 doses per week is 719 fmol/punch (Castillo-Mancilla et al., 2013). In iPrEx OLE, the protective levels of TFV-DP in DBS were quantified as 700 fmol/punch (Grant et al., 2014), that is, there were no infections at visits where TFV-DP concentration was 700 fmol/punch or greater. Current knowledge about PrEP in women indicates consistent use of 6-7 doses a week is required to achieve protection. The lower quartile of simulated TFV-DP levels in DBS at 6 doses per week is 1064 fmol/punch (Castillo-Mancilla et al., 2013). Therefore, we will define effective PrEP use as 700 fmol/punch or more for men, and 1,000 fmol/punch or more for women. Ongoing work with calibration of DBS from directly observed dosing studies may refine these thresholds.

11.4.1 DBS sampling plan

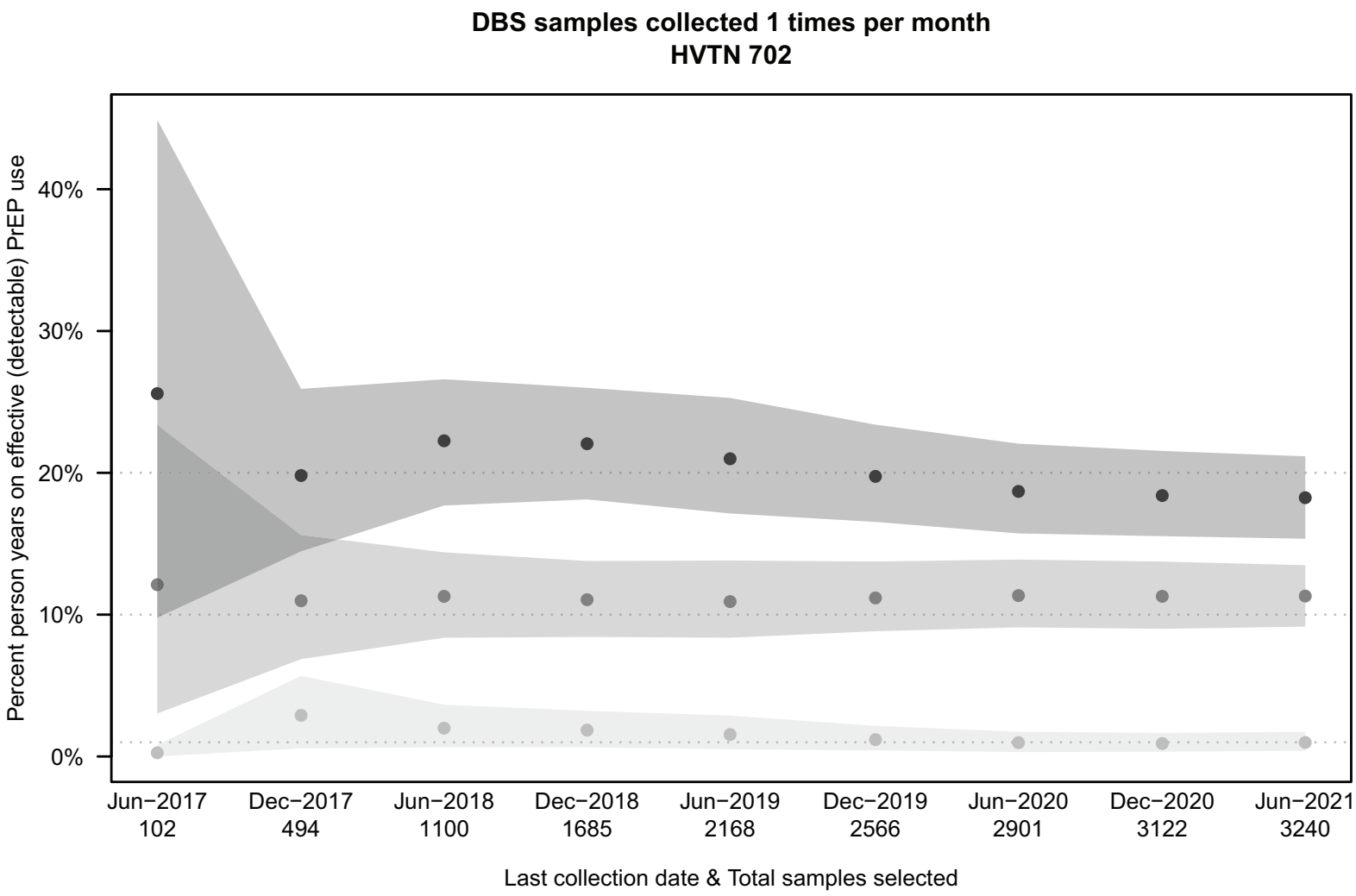
The proposed PrEP monitoring plan of collecting DBS samples on 1 day each month to estimate FTC/TDF prevalence is evaluated using simulations where DBS samples are only collected on certain days of each calendar month. Specifically, we compare plans that collect samples on 1 day each month, 2 days each month, or 3 days each month.

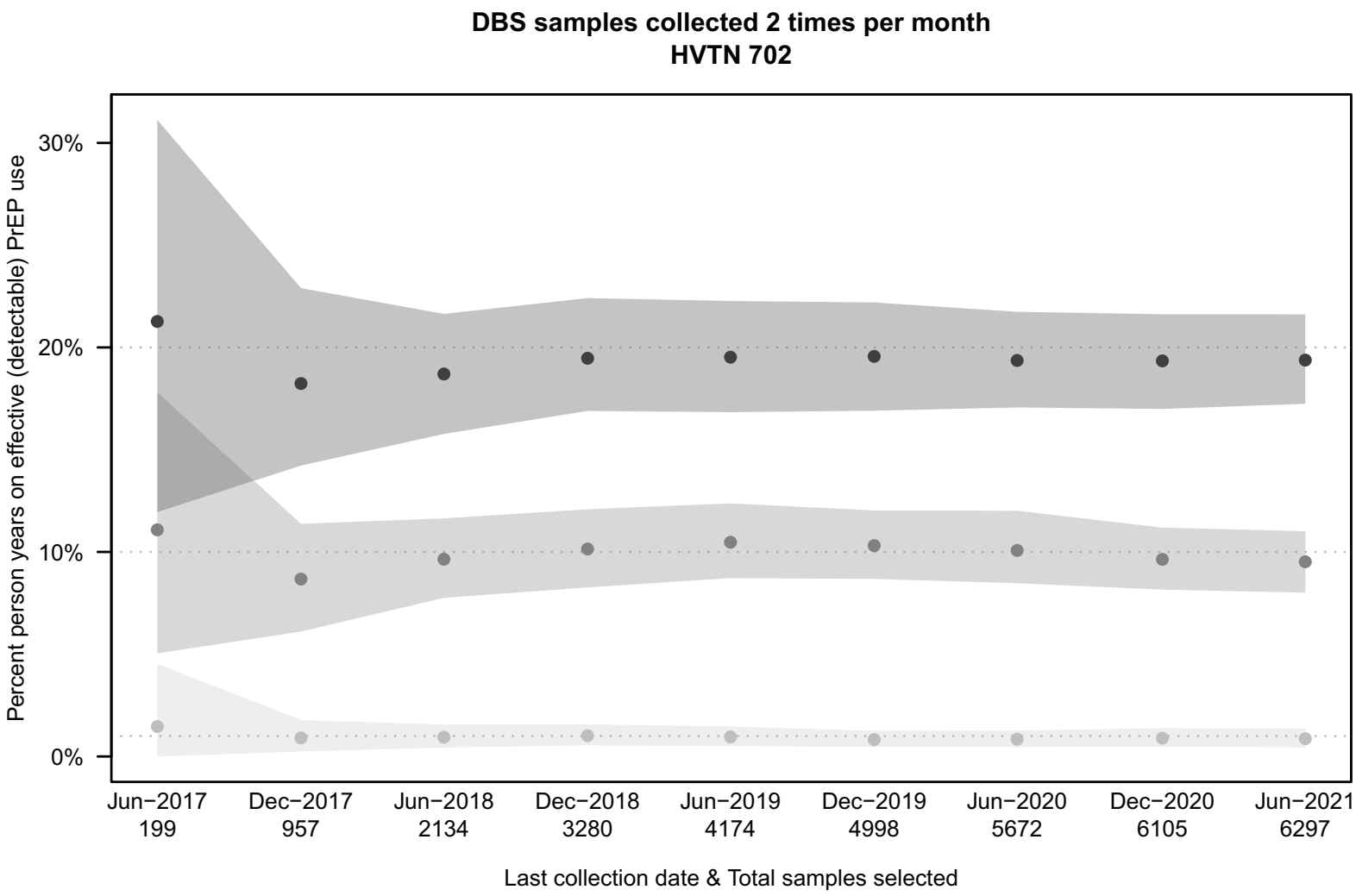
The following are assumed in the simulations: 1) DBS samples are only collected on specific

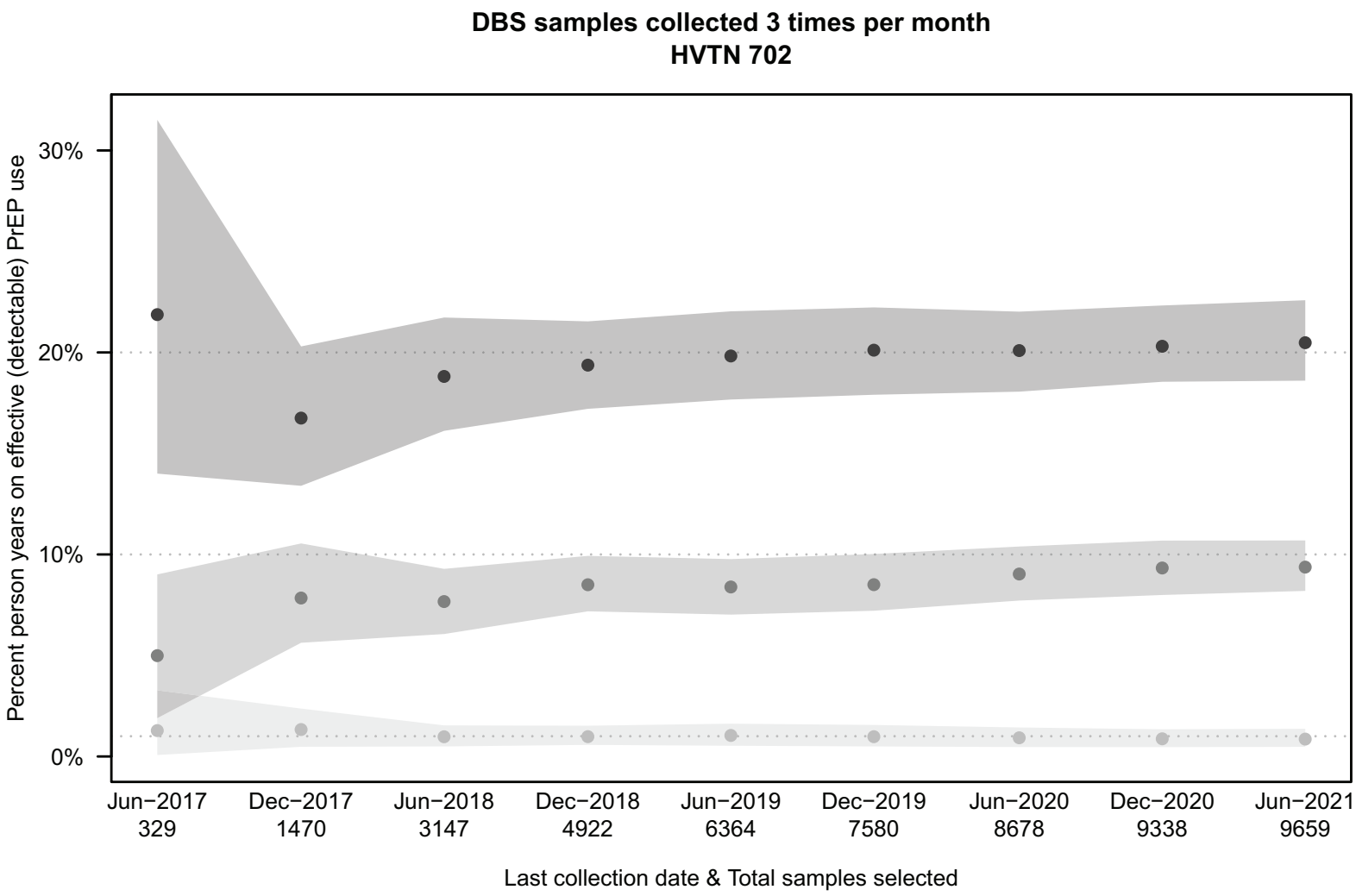
days of each calendar month (we compare plans to assay samples collected on the 10th, 15th, and 20th day of each month); 2) Enrollment falls randomly between Monday and Friday; 3) Follow-up visits follow the visit schedule exactly; 4) Missed visits are distributed uniformly at a rate of 10%; 5) Dropout is 5% per person year and follows an exponential distribution; 6) HIV-infection (in the absence of PrEP) in the placebo group is 4% per person year and follows an exponential distribution; 7) Initiation of DBS sample collection begins by May 2017; 8) Samples are collected and assayed at 6 month intervals, and approximately 3.5 months before each 6-monthly DSMB meeting. Prevalence of FTC/TDF use (either detectable or effective use) was set 1%, 10%, and 20% per person-year. For these simulations, participants are assumed to be either on (or off) FTC/TDF during the entire trial; however the methods for estimating FTC/TDF prevalence are valid and accommodate other extremes such as all participants using PrEP a fraction of the time, or any other pattern of PrEP use.

Simulation results are shown in the following figures corresponding to plans that assay samples on 1, 2, or 3 specific days per month. Each figure shows the 95% confidence interval around the FTC/TDF prevalence that would be observed at each 6-monthly DSMB meeting, assuming 1%, 10%, and 20% FTC/TDF prevalence. Below each date is the total number of samples that would be assayed according to the simulation study. Estimates are shown as dots of varying color intensity corresponding to the three PrEP use scenarios. Corresponding color bands are used to show the 95% bootstrap confidence interval for each estimate. The results show that at the 2017 DSMB meetings, there is a modest gain in precision associated with more frequent sampling. However by the 3rd DSMB meeting in July 2018, the gain in precision due to assaying more samples is limited.

The proposed plan is chosen for the following reasons. The gain in precision of the PrEP prevalence estimate from 2018 onwards with twice or three times a month collection does not justify the increase in cost and burden on the sites. During 2017, PrEP prevalence is estimated with less precision given once-monthly vs. twice- or thrice-monthly sampling; however we expect low PrEP prevalence during this time period, and low PrEP prevalence will have minimal impact on placebo-group HIV incidence. Thus, it is acceptable to have less precision for PrEP prevalence estimates early on in the trial.


DBS samples collected 1 times per month
HVTN 702
Percent person years on effective (detectable) PrEP use
40%
30%
20%
10%
0%
Jun−2017
102
Dec−2017
494
Jun−2018
1100
Dec−2018
1685
Jun−2019
2168
Dec−2019
2566
Jun−2020
2901
Dec−2020
3122
Jun−2021
3240
Last collection date & Total samples selected


DBS samples collected 2 times per month
HVTN 702
Percent person years on effective (detectable) PrEP use
30%
20%
10%
0%
Jun−2017
199
Dec−2017
957
Jun−2018
2134
Dec−2018
3280
Jun−2019
4174
Dec−2019
4998
Jun−2020
5672
Dec−2020
6105
Jun−2021
6297
Last collection date & Total samples selected


DBS samples collected 3 times per month
HVTN 702
Percent person years on effective (detectable) PrEP use
30%
20%
10%
0%
Jun−2017
329
Dec−2017
1470
Jun−2018
3147
Dec−2018
4922
Jun−2019
6364
Dec−2019
7580
Jun−2020
8678
Dec−2020
9338
Jun−2021
9659
Last collection date & Total samples selected

11.4.2 PrEP/PEP monitoring based on self-reported PrEP/PEP data

The number and percentage of participants who self-report PrEP/PEP use will be reported overall and by sex at birth, cross-tabulated by detectable PrEP/PEP use by DBS data. In addition, the number and percentage of males and females who self-report PrEP and PEP use at any point during the study will be tabulated, separately for PrEP and PEP use. Additional information on the number of participants currently using PrEP and the total number of courses of PEP reported by PEP users, each stratified by sex at birth, may be provided during the DSMB open session.

11.4.3 PrEP monitoring based on DBS data

At a given calendar time T (e.g., a fixed date prior to a scheduled DSMB meeting), we are interested in the population-level parameter, percent person-years at-risk for HIV on effective PrEP use between initiation of DBS storage, and time T. Definition of this parameter makes the assumption that we have an assay readout from stored samples that accurately measures effective PrEP use as a binary outcome at the time the sample was drawn; importantly it does not require an accurate measurement of effective PrEP use the day before or for any period of time earlier than the sampling day. In addition to estimating percent person-years on effective PrEP use we define a similar parameter, percent person-years exposed to detectable PrEP using the lower limit of quantitation (LLOQ) of the DBS assay.

Define the target parameter of interest as

$$\Phi(T) = \frac{\int_{T_0}^{T} p(t)E[Y(t)]dt}{\int_{T_0}^{T} E[Y(t)]dt}$$

where T_0 is the time since the first person enrolled after DBS storage commenced, $p(t)$ is the percent of participants on effective PrEP use at time $t \in [T_0, T]$, and $E[Y(t)]$ is the expected number of participants with DBS storage at-risk for HIV at time t.

We estimate $\Phi(T)$ based on the binary PrEP use readout from the DBS assay and the DBS sampling plan. Let i ranging from 1 to N index study participants and let j ranging from 1 to M_i index participant serum collection dates that are sampled for assaying. For each sample collected, we have an indicator x_{ij} of effective PrEP use which is only measured if the DBS sampling indicator, Δ_{ij}, is equal to 1. The estimated percent person-years on effective PrEP use from the initiation of PrEP monitoring time T_0 until time T is defined as

$$\widehat{\Phi}(T) = \frac{\Sigma_{i=1}^{N}\Sigma_{j=1}^{M_i}\Delta_{ij}x_{ij}\pi_{ij}^{-1}P_{ij}}{\Sigma_{i=1}^{N}\Sigma_{j=1}^{M_i}P_{ij}}$$

where the sampling probability, π_{ij}, and person-years, P_{ij}, are defined below.

Let k ranging from 1 to K index the DBS sampling plan collection intervals $[T_0, T_1]$, $(T_1, T_2]$, ..., $(T_{K-1}, T_K]$ where the right endpoint of each interval is a sample collection date (with

$T_K \equiv T$) and define $\mathcal{T}_k$ as the k^{th} interval. Let $t_{i1} < t_{i2} < \ldots < t_{iM_i}$ be the sampling times in $[T_0, T]$ for the i^{th} participant and define t_{i0} as the maximum of T_0 and the i^{th} participants enrollment time. The DBS sampling plan determines which samples, collectively across participants, will be assayed for PrEP use. Define the set of samples, S_{ij}, as all samples collected during the same collection interval $\mathcal{T}_k$ as the sample i, j. That is, $S_{ij} \equiv \{i', j' | t_{i'j'} \in \mathcal{T}_k \text{ for } k \text{ s.t. } t_{ij} \in \mathcal{T}_k\}$. Define the sampling probability as

$$\pi_{ij} \equiv \frac{\Sigma_{i',j' \in S_{ij}} \Delta_{i'j'}}{|S_{ij}|}$$

where $|S_{ij}|$ is the number of samples in set S_{ij}. Define person-years, P_{ij}, as $t_{ij} - t_{i(j-1)}$. We will report bootstrap 95% confidence intervals for $\Phi(T)$. The same approach is used for point and confidence interval estimation of the percent person-years exposed to detectable PrEP use. An example of PrEP use report statistics are shown in Table 4.

Table 4: Estimated rates of PrEP use and estimated percent person-years on effective PrEP use

Number of DBS specimens collected over the 1st batch period	N_1
Number of DBS specimens assayed over the 1st batch period	N_2
Proportion of assayed specimens with TFV-DP above LLOQ (95% CI)	N_3/N_2 (x.xx, x.xx)
Proportion of assayed specimens with TFV-DP above effective use threshold* (95% CI)	N_4/N_2 (x.xx, x.xx)
Percent person years on detectable PrEP through date T=xx (95% CI)#	$\widehat{\Phi}(T)_d$ (x.xx, x.xx)
Percent person years on effective PrEP through date T=xx (95% CI)#	$\widehat{\Phi}(T)_e$ (x.xx, x.xx)
Repeat through N^{th} batch period	

*threshold defined by sex-at-birth (700 fmol/punch in men, 1000 fmol/punch in women)
#$\widehat{\Phi}(T)_d$ is an estimate of the target parameter of interest based on measured TFV-DP above the LLOQ. Similarly, $\widehat{\Phi}(T)_e$ is based on TFV-DP above the study specific threshold for effective PrEP use.

11.5 Performance Standards for Quality of Trial Conduct

The protocol team and study investigators will have performance standards regarding the quality of trial conduct in addition to the study event rate. Some of these standards will relate to achievement of targeted levels of:

1. Participant enrollment into the trial (targets based on protocol assumptions);
2. Adherence to study interventions (target 95% adherence, with minimally acceptable level of 80%);
3. Retention of participants (target 5% annual dropout or less, with minimally acceptable level of no more than 10% annual dropout).

The DSMB and the HVTN 702 leadership will monitor whether the trial is achieving at least minimally acceptable levels of key performance standards. The DSMB will make recommendations to improve areas that are deficient. Termination of the trial would be considered if it appears unlikely that minimally acceptable performance will be achieved.

12 Statistical Software

All analyses described in this SAP will be conducted in *R* and *SAS*.

13 Roles of study statisticians

HVTN SDMC statisticians will be blinded or unblinded to study treatment. During protocol development and after primary follow-up is completed, there will be no distinction between the roles; both types of statisticians will be responsible for designing and analyzing the study. During the primary follow-up period, however, only the unblinded statisticians will see interim data broken down by treatment arm. Their role will be to conduct the interim monitoring and to produce and present reports on accruing data to the study DSMB. During the primary follow-up period, blinded statisticians will see only the interim data pooled across treatment arms. This way, blinded statisticians can assist protocol leadership in making decisions about modifications to the protocol without being influenced by interim efficacy results.

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Appendix

- DSMB open session table shells
- DSMB closed session table shells

DRAFT

HVTN 702

Data and Safety Monitoring Board (DSMB)
OPEN Report
All Tables

Tables and Figures

Table ENROLL1. Enrollment by Study Site

Duration of accrual calculated as activation date through [Date].

Site*	Target	Total Enrolled	Activation Date	First Enrollment Date	Most Recent Enrollment Date	Duration of Accrual (Weeks)	Average per week
Brits	xxx	xxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxx.x	x.x
Cape Town - Emavundleni	xxx	xxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxx.x	x.x
Cape Town - Khayelitsha	xxx	xxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxx.x	x.x
Durban - eThekwini	xxx	xxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxx.x	x.x
Durban - Isipingo	xxx	xxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxx.x	x.x
Durban - Verulam	xxx	xxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxx.x	x.x
Klerksdorp	xxx	xxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxx.x	x.x
Ladysmith	xxx	xxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxx.x	x.x
Medunsa	xxx	xxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxx.x	x.x
Mthatha	xxx	xxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxx.x	x.x
Rustenburg	xxx	xxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxx.x	x.x
Soshanguve	xxx	xxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxx.x	x.x
Soweto - Bara	xxx	xxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxx.x	x.x
Soweto - Kliptown	xxx	xxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxx.x	x.x
Tembisa	xxx	xxx	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	xxx.x	x.x
	xxxx	**xxxx**	**ddMMMyyyy**	**ddMMMyyyy**	**ddMMMyyyy**	**xxx.x**	**xx.x**

Sites shown ordered alphabetically.
*Only activated sites are included

Table ENROLL2. Disposition of Study Participants – Overall and by Study Site

	Total	Soweto - Bara	Soshanguve	Durban - Verulam	Cape Town - Emavundleni	Tembisa	Cape Town - Khayelitsha
Number Randomized	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Enrolled*	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Enrolled	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Pending Enrollment	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Number Enrolled*	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
On Study	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Completed Study	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Off Study Early	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

*Enrolled implies receipt of the first vaccination.
HIV-infected participants who have completed follow-up are reported as On Study, in order to obscure their numbers.

Table BL1. Baseline Participant Characteristics – Overall and by Study Site

	Total	Soweto - Bara	Soshanguve	Durban - Verulam	Cape Town - Emavundleni	Tembisa	Cape Town - Khayelitsha
Total Enrolled	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Sex at Birth							
Male	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Female	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Gender Identity^							
Male	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Female	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Transgender Male	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Transgender Female	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Gender Variant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Self-identify	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Prefer Not to Answer	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Age (Years)							
18 – 20	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
21 – 30	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
31 – 40	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Median (Min, Max)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Race							
White	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Black or African American	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Asian	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indian	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Colored/Mixed	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Multi-racial	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

^Participants may self-report more than one gender identity, thus numbers may total to more than 100%.

Table BL2. Baseline Risk Behaviors for Females – Overall and by Study Site

	Total	Soweto - Bara	Soshanguve	Durban - Verulam	Cape Town - Emavundleni	Tembisa	Cape Town - Khayelitsha
Total Enrolled	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Number Sex Partners in the Last Month							
0	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
3-4	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
>=5	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Median (Min, Max)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Condom use							
Always	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Sometimes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Never	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Anal Sex							
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Had an HIV+ Partner							
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unprotected Sex with HIV+ Partner							
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Exchange of Sex for Money/Gifts							
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Diagnosed with or treated for an STI							
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Alcohol Use and Unprotected Sex							
Never	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
1-2 times	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
3-5 times	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
6 or more times	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Participants are not required to answer risk behavior questions, thus numbers and percentages may not total 100% of enrolled participants.

Table BL3. Baseline Risk Behaviors for Males – Overall and by Study Site

	Total	Soweto - Bara	Soshanguve	Durban - Verulam	Cape Town - Emavundleni	Tembisa	Cape Town - Khayelitsha
Total Enrolled	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Number Sex Partners in the Last Month							
0	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
3-4	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
>=5	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Median (Min, Max)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Condom use							
Always	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Sometimes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Never	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Anal Sex							
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Had an HIV+ Partner							
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unprotected Sex with HIV+ Partner							
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Exchange of Sex for Money/Gifts							
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Diagnosed with or treated for an STI							
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Alcohol Use and Unprotected Sex							
Never	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
1-2 times	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
3-5 times	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
6 or more times	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Participants are not required to answer risk behavior questions, thus numbers and percentages may not total 100% of enrolled participants.

Table STATUS1. Study Status and Reasons for Early Study Termination – Overall and by Study Site

	Total	Soweto - Bara	Soshanguve	Durban - Verulam	Cape Town - Emavundleni	Tembisa	Cape Town - Khayelitsha
Total Enrolled	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Status*							
On Study, In Trt Phase	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
On Study, Completed Trt Phase	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
On Study, Discontinued Trt	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Completed Study, Completed Trt Phas	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Completed Study, Discontinued Trt	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Off Study Early, Completed Trt Phase	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Off Study Early, Discontinued Trt	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Reasons for Early Study Termination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Death	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Participant refused further participation	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unable to adhere to visit schedule	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Participant relocated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unable to contact	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Investigator decision	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Inappropriate enrollment	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Duplicate screening/enrollment	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Early study closure	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Participant incarcerated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Early Study Termination Due to an AE	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

*Participants who discontinued treatment due to HIV infection are reported as 'In Trt Phase' or 'Completed Trt Phase' in order to obscure their numbers.

Table STATUS2. Vaccination Status and Reasons for Discontinuation – Overall and by Study Site

	Total	Soweto - Bara	Soshanguve	Durban - Verulam	Cape Town - Emavundleni	Tembisa	Cape Town - Khayelitsha
Vaccination Status							
In Trt Phase[1]	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Completed Trt Phase	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Discontinued Trt[2]	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Reasons for Discontinuation of Vacc.[2]	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Death	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Adverse Experience	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Reactogenicity Symptom	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other Clinical Event	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unable to Contact / Out of Window	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Participant Refused Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missing	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

[1]Also include participants who discontinued vaccinations due to HIV infection, in order to obscure their numbers.
[2]Excludes discontinuations due to HIV infection.

Table RETEN1. Visit Retention – Overall and by Study Site

	Total	Soweto - Bara	Soshanguve	Durban - Verulam	Cape Town - Emavundleni	Tembisa	Cape Town - Khayelitsha
Participants Enrolled	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Month 1 / Vaccination 2							
Expected for Visit	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently Discontinued Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 3 / Vaccination 3							
Expected for Visit	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently Discontinued Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 6 / Vaccination 4							
Expected for Visit	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently Discontinued Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 6.5 / Post-Vaccination							
Expected for Visit	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently Discontinued Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 12 / Vaccination 5							
Expected for Visit	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
.	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
.							
.							

For computing visit retention, participants are considered expected for a visit when they reach the end of their visit window.

Table RETEN2. Vaccination Adherence – Overall and by Study Site

	Total	Soweto - Bara	Soshanguve	Durban - Verulam	Cape Town - Emavundleni	Tembisa	Cape Town - Khayelitsha
Total Enrolled	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Month 1 / Vaccination 2							
Retained	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Received Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 3 / Vaccination 3							
Retained	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Received Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 6 / Vaccination 4							
Retained	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Received Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 12 / Vaccination 5							
Retained	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Received Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Retained = # participants who completed the visit
A visit is considered completed once the Post-Enrollment Vaccination or Specimen Collection form is entered in the study database.

Table RE1. Maximum Local Reactogenicity Summary by Vaccination

Number of Enrolled Participants = xxxx
Cohort: Safety cohort

	All Vaccinations N=xxx n %	Vacc 1 N=xxx n %	Vacc 2 N=xxx n %	Vacc 3 N=xxx n %	Vacc 4 N=xxx n %	Vacc 5 N=xxx n %
Pain						
None	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)
Mild	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Moderate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life-Threatening	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Tenderness						
None	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)
Mild	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Moderate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life-Threatening	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Pain and/or Tenderness						
None	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)
Mild	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Moderate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life-Threatening	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Erythema						
.						
.						
.						

Events are noted in the category of highest severity grade reported.

Table RE2. Maximum Systemic Reactogenicity Summary by Vaccination

Number of Enrolled Participants = xxxx
Cohort: Safety cohort

	All Vaccinations N=xxx n %	Vacc 1 N=xxx n %	Vacc 2 N=xxx n %	Vacc 3 N=xxx n %	Vacc 4 N=xxx n %	Vacc 5 N=xxx n %
Malaise and/or Fatigue						
None	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)
Mild	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Moderate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life-Threatening	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Myalgia						
None	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)
Mild	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Moderate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life-Threatening	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Headache						
None	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)
Mild	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Moderate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life-Threatening	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Nausea						
None	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)	xxxx (xx.x%)
Mild	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
.						
.						
.						

Events are noted in the category of highest severity grade reported.

Table EAE1. Expedited Adverse Events (EAEs) Reported to the Regulatory Support Center (RSC) by Participant and Decreasing Severity

Publication ID	Severity	EAE Number	Adverse Experience	Onset Date	Relation to Vaccine	Medical Officer's Relation to Vaccine	Number of Previous Vacc.	Days Since Last Vacc.
XXX-XXXX	**text**	**XXXXXX**	**text**	**ddMMMyyyy**	**text**	**text**	**X**	**XX**
XXX-XXXX	text	XXXXXX	text	ddMMMyyyy	text	text	X	XX
XXX-XXXX	text	XXXXXX	text	ddMMMyyyy	text	text	X	XX
.								
.								
.								
.								
XXX-XXXX	**text**	**XXXXXX**	**text**	**ddMMMyyyy**	**text**	**text**	**X**	**XX**
XXX-XXXX	**text**	**XXXXXX**	**text**	**ddMMMyyyy**	**text**	**text**	**X**	**XX**
XXX-XXXX	text	XXXXXX	text	ddMMMyyyy	text	text	X	XX

Records shown in bold face are new to this report.

Table AE1. Grade 2-5 Adverse Events (AEs) by System Organ Class, Sorted by Decreasing Frequency

Cohort: Safety cohort (N = xxxx)

System Organ Class	n	Incidence
Infections and infestations	xxx	xx.x%
Gastrointestinal disorders	xxx	xx.x%
General disorders and administration Country conditions	xxx	xx.x%
Respiratory, thoracic and mediastinal disorders	xxx	xx.x%
Injury, poisoning and procedural complications	xxx	xx.x%
Musculoskeletal and connective tissue disorders	xxx	xx.x%
Skin and subcutaneous tissue disorders	xxx	xx.x%
Nervous system disorders	xxx	xx.x%
Psychiatric disorders	xxx	xx.x%
Investigations	xxx	xx.x%
Vascular disorders	xxx	xx.x%
Reproductive system and breast disorders	xxx	xx.x%
Metabolism and nutrition disorders	xxx	xx.x%
Eye disorders	xxx	xx.x%
Blood and lymphatic system disorders	xxx	xx.x%
Renal and urinary disorders	xxx	xx.x%
Immune system disorders	xxx	xx.x%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	xxx	xx.x%
Ear and labyrinth disorders	xxx	xx.x%
Cardiac disorders	xxx	xx.x%
Endocrine disorders	xxx	xx.x%
Hepatobiliary disorders	xxx	xx.x%
Social circumstances	xxx	xx.x%
Surgical and medical procedures	xxx	xx.x%

n's are the number of participants reporting one or more AEs within a specific system organ class.
Incidence is calculated by n divided by the number enrolled x 100.
AE records included in the table have been coded into MedDRA codes by SCHARP clinical staff.

Table AE2. Grade 2-5 Adverse Events (AEs) by System Organ Class, High Level Term, and Severity

Cohort: Safety cohort (N = xxxx)

	>= Moderate	>= Severe	>= Life Threatening	Fatal
System Organ Class/High Level Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Participants with one or more AEs	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Blood and lymphatic system disorders	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Anaemia	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lymphadenopathy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gastrointestinal disorders	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Diarrhoea	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Food poisoning	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Vomiting	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Infections and infestations	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Bronchitis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gastroenteritis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Herpes simplex	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Nasopharyngitis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Sinusitis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Viral infection	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
.				
.				
.				

n's are the number of participants reporting one or more AEs within a specific system organ class.
Incidence is calculated by n divided by the number enrolled x 100.
AE records included in the table have been coded into MedDRA codes by SCHARP clinical staff.

Table AE3. Grade 2-5 Adverse Events (AEs) Related to Study Product by System Organ Class, High Level Term, and Severity

Cohort: Safety cohort (N = xxxx)

	>= Moderate	>= Severe	>= Life Threatening	Fatal
System Organ Class/High Level Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Participants with one or more related AEs	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Blood and lymphatic system disorders	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Anaemia	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lymphadenopathy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gastrointestinal disorders	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Diarrhoea	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Food poisoning	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Vomiting	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Infections and infestations	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Bronchitis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gastroenteritis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Herpes simplex	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Nasopharyngitis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Sinusitis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Viral infection	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
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n's are the number of participants reporting one or more related AEs within a specific system organ class.
Incidence is calculated by n divided by the number enrolled x 100.
AE records included in the table have been coded into MedDRA codes by SCHARP clinical staff.

Table SI1. Social Impact Summary of Events

Number of Enrolled Participants = XXX

	Number of SI Events	Impact of SI Event on Quality of Life				Resolution Status		
		None n (%)	Minimal n (%)	Moderate n (%)	Major n (%)	Resolved n (%)	Unable to Resolve n (%)	Unresolved n (%)
All Social Impacts	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Types of Social Impacts								
Personal Relationships	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Travel/Immigration	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Employment	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Education	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medical/Dental	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Health Insurance/Medical Aid/Hospital Plan	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Life Insurance/Funeral Cover	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Housing	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Military/Other Gov Agency	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Beneficial Impact	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

The denominator for all percentages is the number of SI events.

Table SI2. Social Impact Summary at Participant Level

Number of Enrolled Participants = XXX

	Number of SI Events	Ppts Reporting SI Events n (%)	Maximum Impact of SI Event on Quality of Life: None n (%)	Minimal n (%)	Moderate n (%)	Major n (%)
All Social Impacts	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Types of Social Impacts						
Personal Relationships	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Travel/Immigration	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Employment	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Education	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medical/Dental	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Health Insurance/Medical Aid/Hospital Plan	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Life Insurance/Funeral Cover	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Housing	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Military/Other Gov Agency	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Beneficial Impact	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

The denominator for all percentages is the number of enrolled participants.

Table PREG1. Pregnancy Listing

Publication ID	LMP Onset Date	Pregnancy Outcome Date	Date Last Vacc. Prior to Outcome	Pregnancy Outcome	Time from Prior Vacc. To LMP	# Vacc. Prior to LMP	# Vacc. Prior to Outcome	Total # Vacc.	Comments
XXX-XXXX	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	text	xx	x	x	xx	
XXX-XXXX	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	text	xx	x	x	xx	
XXX-XXXX	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	text	xx	x	x	xx	
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XXX-XXXX	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	text	xx	x	x	xx	
XXX-XXXX	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	text	xx	x	x	xx	
XXX-XXXX	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	text	xx	x	x	xx	

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Table ENROLL1. Disposition of Study Participants, by Treatment Assignment

	Total		A		B	
Number Randomized	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Enrolled*	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Not Enrolled	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Pending Enrollment	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Number Enrolled*	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
On Study	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Completed Study	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Off Study Early	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)

*Enrolled implies receipt of the first vaccination.

Table BL1. Baseline Participant Characteristics, by Treatment Assignment

	Total	A	B
Total Enrolled	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Sex at Birth			
Male	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Female	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Gender Identity^			
Male	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Female	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Transgender Male	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Transgender Female	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Gender Variant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Self-identify	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Prefer Not to Answer	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Age (Years)			
18 – 20	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
21 – 30	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
31 – 40	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Median (Min, Max)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Race			
White	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Black or African American	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Asian	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Indian	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Colored/Mixed	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Multi-racial	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

^Participants may self-report more than one gender identity, thus numbers and percentages may total to more than 100%.

Table BL2. Baseline Risk Behaviors for Females, by Treatment Assignment

	Total	A	B
Total Enrolled	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Number of Sex Partners in the Last Month			
0	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
3-4	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
>=5	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Median (Min, Max)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Condom use			
Always	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Sometimes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Never	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Anal Sex			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Had an HIV+ Partner			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unprotected Sex with HIV+ Partner			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Exchange of Sex for Money/Gifts			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Diagnosed with or treated for STI			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Alcohol Use and Unprotected Sex			
Never	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
1-2 times	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
3-5 times	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
6 or more times	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Participants are not required to answer risk behavior questions, thus numbers and percentages may not total 100% of enrolled participants.

Table BL3. Baseline Risk Behaviors for Males, by Treatment Assignment

	Total	A	B
Total Enrolled	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Number of Sex Partners in the Last Month			
0	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
3-4	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
>=5	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Median (Min, Max)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Condom use			
Always	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Sometimes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Never	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Anal Sex			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Had an HIV+ Partner			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unprotected Sex with HIV+ Partner			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Exchange of Sex for Money/Gifts			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Diagnosed with or treated for STI			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Alcohol Use and Unprotected Sex			
Never	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
1-2 times	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
3-5 times	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
6 or more times	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Participants are not required to answer risk behavior questions, thus numbers and percentages may not total 100% of enrolled participants.

Table STATUS1. Study Status and Reasons for Early Study Termination, by Treatment Assignment

	Total		A		B	
Total Enrolled	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Status*						
On Study, In Trt Phase	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
On Study, Completed Trt Phase	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
On Study, Discontinued Trt	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Completed Study, Completed Trt Phas	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Completed Study, Discontinued Trt	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Off Study Early, Completed Trt Phase	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Off Study Early, Discontinued Trt	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Reasons for Early Study Termination	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Death	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Participant refused further participation	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Unable to adhere to visit schedule	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Participant relocated	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Unable to contact	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Investigator decision	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Inappropriate enrollment	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Duplicate screening/enrollment	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Early study closure	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Participant incarcerated	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Other	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Early Study Termination Due to an AE	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)

Table STATUS2. Vaccination Status and Reasons for Discontinuation, by Treatment Assignment

	Total	A	B
Vaccination Status			
In Trt Phase	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Completed Trt Phase	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Discontinued Trt	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Reasons for Discontinuation of Vacc.	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Death	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Adverse Experience	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Reactogenicity Symptom	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other Clinical Event	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unable to Contact / Out of Window	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Participant Refused Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missing	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Table RETEN1. Visit Retention, by Treatment Assignment

	Total	A	B
Total Enrolled	xxx	xxx	xxx
Month 1 / Vaccination 2			
Expected for Visit	xxx	xxx	xxx
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently Discontinued Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 3 / Vaccination 3			
Expected for Visit	xxx	xxx	xxx
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently Discontinued Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 6 / Vaccination 4			
Expected for Visit	xxx	xxx	xxx
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently Discontinued Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 6.5 / 2 Weeks Post Vaccination 4			
Expected for Visit	xxx	xxx	xxx
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently Discontinued Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 9 / 3 Months Post Vaccination 4			
Expected for Visit	xxx	xxx	xxx
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently Discontinued Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 12 / Vaccination 5			
Expected for Visit	xxx	xxx	xxx
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently Discontinued Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 12.5 / 2 Weeks Post Vaccination 5			
Expected for Visit	xxx	xxx	xxx
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
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.			

Post-vaccination visits are not expected if the vaccination visit was not done.
Retained = # participants who completed the visit.
A visit is considered expected if the participant is in Schedule 1 and the visit window has closed.
A visit is considered completed once the Post-Enrollment Vaccination or Specimen Collection form is entered in the study database.
Participants who discontinue and terminate at the same visit are marked as terminated for the visit.

Table RETEN2. Vaccination Adherence, by Treatment Assignment

	Total	A	B
Total Enrolled	xxx	xxx	xxx
Month 1 / Vaccination 2			
Retained	xxx	xxx	xxx
Received Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 3 / Vaccination 3			
Retained	xxx	xxx	xxx
Received Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 6 / Vaccination 4			
Retained	xxx	xxx	xxx
Received Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 12 / Vaccination 5			
Retained	xxx	xxx	xxx
Received Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Vaccination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Retained = # participants who completed the visit
A visit is considered completed once the Post-Enrollment Vaccination or Specimen Collection form is entered in the study database.

Table RE1. Maximum Local Reactogenicity Summary, by Treatment Assignment

Cohort: Safety cohort

	Total		A		B	
Number Vaccinated	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Pain						
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Tenderness						
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Pain and/or Tenderness						
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Erythema						
None or not gradeable	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
6.25 to < 25 cm^2 or 2.5 to <5 cm single dim (Gr 1)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
25 to < 100 cm^2 or 5 to <10 cm single dim (Gr2)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
>= 100 cm^2 or >= 10 cm single dim or severe complication (Gr 3)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
> Life threatening complication (Gr 4)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
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Events are noted in the category of highest severity grade reported.

Table RE2. Maximum Systemic Reactogenicity Summary, by Treatment Assignment

Cohort: Safety cohort

	Total		A		B	
Number Vaccinated	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Malaise and/or Fatigue						
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Myalgia						
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Headache						
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Nausea						
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
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Events are noted in the category of highest severity grade reported.

Table EAE1. Expedited Adverse Events (EAEs) Reported to the Regulatory Support Center (RSC) Listed by Treatment Assignment, Participant, and Decreasing Severity

Trt.	Publication ID	Severity	EAE Number	Adverse Experience	Onset Date	Relation to Vaccine	Medical Officer's Relation to Vaccine	Number of Previous Vacc.	Days Since Last Vacc.
A	XXX-XXXX	text	XXXXXX	text	ddMMMyyyy	text	text	X	XX
	XXX-XXXX	text	XXXXXX	text	ddMMMyyyy	text	text	X	XX
	XXX-XXXX	text	XXXXXX	text	ddMMMyyyy	text	text	X	XX
	.								
	.								
	.								
	.								
B	XXX-XXXX	text	XXXXXX	text	ddMMMyyyy	text	text	X	XX
	XXX-XXXX	text	XXXXXX	text	ddMMMyyyy	text	text	X	XX
	XXX-XXXX	text	XXXXXX	text	ddMMMyyyy	text	text	X	XX

Table AE1. Grade 2-5 Adverse Events (AEs) by System Organ Class, Severity, and Treatment Assignment, Sorted by Decreasing Frequency

Cohort: Safety cohort

	Total (N=XXXX)		A (N=XXXX)		B (N=XXXX)	
System Organ Class/ Severity	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Participants with one or more AEs						
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Infections and infestations						
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Gastrointestinal disorders						
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
General disorders and administration Country conditions						
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Musculoskeletal and connective tissue disorders						
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Injury, poisoning and procedural complications						
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Respiratory, thoracic and mediastinal disorders						
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
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n's are the number of participants reporting one or more AEs within a specific system organ class.
Incidence is calculated by n divided by the number enrolled x 100.
AE records included in the table have been coded into MedDRA codes by SCHARP clinical staff.

Table AE2. Grade 2-5 Adverse Events (AEs) by High Level Term, Severity, and Treatment Assignment, Sorted by Decreasing Frequency

Cohort: Safety cohort

	Total (N=XXXX) n (%)	A (N=XXXX) n (%)	B (N=XXXX) n (%)
Participants with one or more AEs			
Moderate and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Upper respiratory tract infections			
Moderate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Streptococcal Infections			
Moderate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Allergies to foods, food additives, drugs and other chemicals			
Moderate and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Abdominal and gastrointestinal infections			
Moderate and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Diarrhea (excl infective)			
Moderate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
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n's are the number of participants reporting one or more AEs within a specific system organ class.
Incidence is calculated by n divided by the number enrolled x 100.
AE records included in the table have been coded into MedDRA codes by SCHARP clinical staff.

Table AE3. Grade 2-5 Adverse Events (AEs) Related to Study Product by High Level Term, Severity, and Treatment Assignment, Sorted by Decreasing Frequency

Cohort: Safety cohort

	Total (N=XXXX)		A (N=XXXX)		B (N=XXXX)	
	n	(%)	n	(%)	n	(%)
Participants with one or more related AEs						
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Upper respiratory tract infections						
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Streptococcal Infections						
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Allergies to foods, food additives, drugs and other chemicals						
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Abdominal and gastrointestinal infections						
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Diarrhea (excl infective)						
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
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.						

n's are the number of participants reporting one or more related AEs within a specific system organ class.
Incidence is calculated by n divided by the number enrolled x 100.
AE records included in the table have been coded into MedDRA codes by SCHARP clinical staff.

Table PREG1. Pregnancy Listing

Trt	Publication ID	LMP Onset Date	Pregnancy Outcome date	Date Last Vacc. Prior to Outcome	Pregnancy Outcome	Time from Prior Vacc. To LMP	# Vacc. Prior to LMP	# Vacc. Prior to Outcome	Total # Vacc.	Comments
	XXX-XXXX	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	text	text	text	X	XX	
	XXX-XXXX	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	text	text	text	X	XX	
	XXX-XXXX	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	text	text	text	X	XX	
	.									
	.									
	.									
	XXX-XXXX	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	text	text	text	X	XX	
	XXX-XXXX	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	text	text	text	X	XX	
	XXX-XXXX	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	text	text	text	X	XX	