STATISTICAL ANALYSIS PLAN

Protocol HVTN 116

A phase 1 clinical trial to evaluate the safety, pharmacokinetics, and anti-viral activity of VRC-HIVMAB060-00-AB (VRC01) and VRC-HIVMAB080-00-AB (VRC01LS) in the serum and mucosa of healthy, HIV-uninfected adult participants

Date: **17 December 2019**

SAP Version 2.0

Prepared by

Protocol Statisticians	**Yunda Huang, PhD**
	Mengshu Shao, MS
	Yiwen Lu, MS

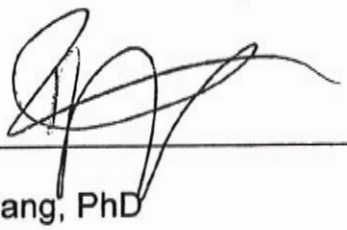
SAP Approval Signature Page

HVTN 116

Statistical Analysis Plan

A phase 1 clinical trial to evaluate the safety, pharmacokinetics, and anti-viral activity of VRC-HIVMAB060-00-AB (VRC01) and VRC-HIVMAB080-00-AB (VRC01LS) in the serum and mucosa of healthy, HIV-uninfected adult participants

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



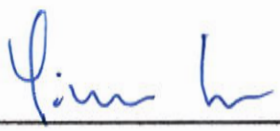
12/26/2019

Yunda Huang, PhD — Date

Principle Staff Scientist

Vaccine and Infectious Disease Division

Fred Hutchinson Cancer Research Center



12/30/2019

Yiwen Lu, MS — Date

Statistical Research Associate

Fred Hutchinson Cancer Research Center, SCHARP

SAP Modification History

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

Date: 7 July 2017
SAP version: Version *0.0*
Modifications: First draft concerning only the analysis of safety endpoints.

Date: 28 Feb. 2018
SAP version: Version *1.0*
Modifications: this version includes the analysis of safety and TLA assay endpoints.

Date: 18 Sep. 2018
SAP version: Version *1.1*
Modifications: this version includes the analysis of safety, TLA assay and mucosal VRC01/VRC01LS levels endpoints.

Date: 17 December 2019
SAP version: Version *2.0*
Modifications:

- Replaced Yiwen Lu as the SRA of the study as Mengshu Shao has left SCHARP.
- Section 7: Clarified the handling of blinding of lab staff to VRC01 or VRC01LS treatment groups for different assays
- Section 8: clarified the handling of out-of-window data
- Section 8.5.2: modified text regarding the analysis of mucosal VRC01/LS level data; added the analysis of ELISA serum concentration data
- Section 10.3: added the lists of tables and figures for the analysis of ELISA serum concentration data

Table of Contents

1. OVERVIEW

The following describes the Statistical Analysis Plan (SAP) for the analysis of safety and immunogenicity data from HVTN 116. As detailed in SCHARP SOP 7.2, Version 4.0 (issue date: August 12, 2004), this SAP is required prior to the first analysis and must be approved by the protocol team chair and the lead protocol statistician. The plan will be reviewed and updated prior to any interim analyses and before the final analysis with all major revisions of the plan archived.

2. PROTOCOL SUMMARY

Title

A phase 1 clinical trial to evaluate the safety, pharmacokinetics, and anti-viral activity of VRC-HIVMAB060-00-AB (VRC01) and VRC-HIVMAB080-00-AB (VRC01LS) in the serum and mucosa of healthy, HIV-uninfected adult participants

Study products and routes of administration

- VRC01: human monoclonal antibody (mAb) VRC-HIVMAB060-00-AB in formulation buffer at pH 5.8 in sufficient normal saline (Sodium Chloride for Injection 0.9%, USP) to be administered intravenously (IV).

- VRC01LS: human monoclonal antibody (mAb) VRC-HIVMAB080-00-AB in formulation buffer at pH 5.8 in sufficient normal saline (Sodium Chloride for Injection 0.9%, USP) to be administered IV.

Participants

- 79 healthy, HIV–uninfected adult volunteers aged 18 to 50 years, regardless of sex or gender

Schema

Group	Treatment	Infusion schedule (Months)					
		N	M0	M2	M3	M4	M6
Group 1	VRC01 10 mg/kg	23	IV Infusion	IV Infusion		IV Infusion	IV Infusion
Group 2	VRC01 30 mg/kg	23	IV Infusion	IV Infusion		IV Infusion	IV Infusion
Group 3	VRC01LS 30 mg/kg	7*	IV Infusion		IV Infusion		IV Infusion
Group 4	VRC01 30 mg/kg	16	IV Infusion				
Group 5	VRC01LS 30 mg/kg	10*	IV Infusion				

**Note:* Groups 1, 2, and 3 will be randomized together. Groups 4 and 5 will be randomized together.

**Note: enrollment has stopped in groups 3 & 5, no more participants will be enrolled to group 3 & 5*

3. OBJECTIVES AND ENDPOINTS

3.1. Primary objective:

Primary objective 1:

- To evaluate the safety and tolerability of VRC01/VRC01LS mAb administered through IV infusion.

Primary endpoints 1:

- Local and systemic reactogenicity, laboratory measures of safety, AEs, SAEs, and rates of discontinuation.

Primary objective 2:

- For each sex at birth, to evaluate the pharmacokinetics of VRC01 in serum versus mucosa in each mucosal compartment.

Primary endpoint 2 (Groups 1 & 2 & 4):

- Serum concentration of VRC01 out to Month 6 after the last infusion.
- Levels of VRC01 in genital and rectal secretions, as well as cervical, vaginal, and rectal tissues at the collection timepoints.

3.2. Secondary objective:

Secondary objective 1:

- To evaluate the ability of the *in vivo*–infused VRC01/VRC01LS antibodies to inhibit HIV-1 infection in tissue explants.

Secondary endpoint 1:

- *Ex vivo* inhibition of HIV-1 infectivity in tissue biopsies in Groups 1 – 3.

3.3. **Exploratory objectives and endpoints**

Exploratory objective 1:

- For each sex at birth, to evaluate the pharmacokinetics of VRC01LS in serum versus mucosa in each mucosal compartment.

Exploratory objective 2:

- To evaluate the levels of VRC01LS in serum, mucosal secretions, and mucosal tissues and those of VRC01 at the 30 mg/kg dose level.

Exploratory objective 3:

- To evaluate the tissue distribution of VRC01/VRC01LS in mucosal biopsies.

Exploratory objective 4:

- To compare the levels and functionality of VRC01/VRC01LS in mucosal secretions and tissues between the cervical, vaginal, and rectal compartments from the same participant.

Exploratory objective 5:

- To assess the relationship between inflammation in mucosal biopsies and levels of antibody in these tissues and related secretions.

Exploratory objective 6:

- To assess the acceptability and tolerability of repeat mucosal sampling, including secretions and biopsies, for application in future studies.

Exploratory objective 7:

- To assess the relationship between Fc receptor genotypes and VRC01/VRC01LS pharmacokinetics and/or ex vivo infectivity of biopsies.

Exploratory objective 8:

- To further evaluate the retention of functional characteristics of in vivo–infused VRC01/VRC01LS in each group, additional assays may be performed, including on samples from other timepoints.

Exploratory objective 9:

- To conduct analyses related to furthering the understanding of HIV, immunology, vaccines, antibody mediated prevention, and clinical trial conduct.

4. COHORT DEFINITION

Participants

79 healthy, HIV–uninfected adult volunteers aged 18 to 50 years, regardless of sex or gender

Design

Multicenter, randomized, placebo controlled, double-blind trial

Duration per participant

As VRC01LS is designed to have a longer half-life than VRC01, participants who receive VRC01 will be followed for 6 months after the last product administration and participants who receive VRC01LS will be followed for 12 months after the last product administration. Specifically,

Groups 1, 2, and 5: 12 months of scheduled clinic visits

Group 3: 18 months of scheduled clinic visits

Group 4: 6 months of scheduled clinic visits

Estimated total study duration

40 months (includes enrollment, and follow-up)

5. POTENTIAL CONFOUNDERS

Characterization of the safety of the vaccine is susceptible to confounding by adverse events not related to the vaccine that by chance occur more often in one arm of the trial than another. Therefore analyses involving adverse events will incorporate the reported relationship to product as assessed by HVTN staff.

6. RANDOMIZATION

The randomization sequence will be obtained by computer-generated random numbers and provided to each HVTN CRS through the SDMC via a Web-based randomization system. Participants will be randomized to either one of Groups 1-3 or one of Groups 4-5, depending on site. The randomization will be stratified by sex at birth and done in blocks to ensure balance across Groups 1-3, and across Groups 4 and 5. All participants will be randomized prior to the first infusion, ideally within 4 days. At each institution, the pharmacist with primary responsibility for dispensing study products is charged with maintaining consistency of the treatment assignments.

After the trial started, the enrollment was capped in Groups 3 and 5 at n=7 and n=10, respectively in November 2017 and December 2017, to limit the number of VRC01LS participants due to the emerging of other more superior mAb products in the field.

7. BLINDING

The study will be open label. Lab staff performing the TLA and Singulex assays will be blinded to group assignments for all groups; lab staff performing the ELISA assay measuring mAb concentrations in serum will be unblinded to assignments to VRC01 or VRC01LS groups.

8. STATISTICAL ANALYSIS

This section describes the final study analysis. Of note, Groups 1-3 participants are enrolled 1 month before the first infusion. Groups 4 and 5 participants are enrolled at the first infusion. All analyses pertaining to the safety and drug level objectives of this study are intent-to-treat analyses that include all randomized individuals per their randomization allocation. In addition, analyses will also be performed as treated accounting for the actual infusions and dose levels each participant received.

No formal multiple comparison adjustments will be employed for multiple safety endpoints.

8.1. Analysis variables

The analysis variables consist of baseline participant characteristic, safety, and laboratory measurements for primary- and secondary-objective analyses.

8.2. Analysis tools

Analyses for primary endpoints will be performed in SAS. All other descriptive and inferential statistical analyses will be performed using SAS, StatXact, S-Plus, and/or R statistical software.

8.3. Baseline comparability

Treatment arms will be compared for baseline participant characteristics using descriptive statistics.

8.4. Safety/tolerability analysis

All participants who received at least 1 partial or complete infusion will provide some safety data.

8.4.1.Reactogenicity

The number and percentage of participants experiencing each type of reactogenicity sign or symptom will be tabulated by severity and treatment arm and the percentages displayed graphically by arm. For a given sign or symptom, each participant's reactogenicity will be counted once under the maximum severity for all infusion visits. In addition, to the individual types of events, the maximum severity of local pain or tenderness, induration or erythema, and of systemic symptoms will be calculated.

8.4.2.AEs and SAEs

AEs will be summarized using MedDRA System Organ Class and preferred terms. Tables will show by treatment arm the number and percentage of participants experiencing an AE within a System Organ Class or within preferred term category by severity or by relationship to study product or mucosal sampling. For the calculations in these tables, a participant with multiple AEs within a category will be counted once under the maximum severity or the strongest recorded causal relationship to study product or mucosal sampling. Formal statistical testing comparing arms is not planned since interpretation of differences must rely heavily upon clinical judgment.

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 or mucosal sampling, time between onset and last infusion, and number of infusions received.

8.4.3.Local laboratory values

Boxplots of local laboratory values will be generated for baseline values and for values measured during the course of the study by treatment arm and visit. Each boxplot will show the first quartile, the median, and the third quartile. Outliers (values outside the boxplot) will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

For each local laboratory measure, summary statistics will be presented by treatment arm and time point, as well as changes from baseline for post-enrollment values. In addition, the number (percentage) of participants with local laboratory values recorded as meeting Grade 1 AE criteria or above as specified in the DAIDS AE Grading Table (see Section 11.2 of the protocol) will be tabulated by treatment arm for each postinfusion time point. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

8.4.4. Reasons for discontinuation of study product administration and early study termination

The number and percentage of participants who discontinue study product administration and who terminate the study early will be tabulated by reason and treatment arm.

8.5. Analyses of mAb concentration and functional responses

8.5.1. General approach

For the statistical analysis of lab endpoints, data from enrolled participants will be used according to the initial randomization assignment regardless of how many infusions they received. Additional analyses may be performed, limited to participants who received all scheduled infusions per protocol. Assay results that are unreliable, or from HIV-infected participants postinfection will be excluded. Since the exact date of HIV infection is unknown, any assay data from blood draws 4 weeks prior to an infected participant's last seronegative sample and thereafter may be excluded. If an HIV-infected participant does not have a seronegative sample postenrollment, then all data from that participant may be excluded from the analysis. Assay results that are from specimens collected outside of the visit window are generally also excluded unless otherwise noted in analyses (e.g., population pharmacokinetics analyses of concentrations over time) that account for the actual date of specimen collection.

For continuous assay data (eg, serum concentration of VRC01), graphical and tabular summaries of the distributions by treatment arm and timepoint will be made. Scatterplot matrix with correlation coefficient information between each pair of serum and mucosa drug levels at different timepoints will be provided. An appropriate data transformation (eg, log transformation) may be applied prior to testing to better satisfy analysis assumptions. Inference from these analyses would be limited by the small sample sizes of the groups.

For qualitative assay variables (eg, positive or negative), the analyses will be performed by tabulating the frequency of positive responses for each assay by group at each timepoint at which an assessment is performed. Crude response rates will be presented with their corresponding 95% confidence interval estimates calculated using the score test method [66].

More sophisticated analyses of drug-level data and other assay data collected over time employing repeated measures methodology that is valid under the missing at random (MAR) assumption (for example, nonlinear mixed effects models) may be utilized to incorporate outcome responses over several timepoints and to account for subject heterogeneity. MAR assumes that the probability of an observation being missing may depend upon the observed responses and upon observed covariates, but not upon any unobserved data. Generalized nonlinear models for response rates will use a binomial error distribution and for quantitative endpoints, a normal error distribution. All models will include as covariates all available baseline predictors of the missing outcomes.

In addition, non-compartment PK analysis will be performed to estimate PK parameters from individual time-concentration curves. The correlation between individual-level PK parameters estimated for different specimen types (serum vs. mucosa) may also be assessed. All statistical tests will be 2-sided and will be considered statistically significant if $p <= 0.05$.

For the analysis of correlation between two continuous assay variables over time, graphical summary and tabular summary of the sample correlation at each given timepoint will be made. Cross-correlation of the 2 variables with different time lags may also be calculated and visually displayed if there are at least 10 participants with no missing data over time from both variables. Nonlinear or linear mixed effects models may also be used to predict mucosal drug levels based on serum drug levels collected at the same or previous timepoints.

8.5.2. Assay-Specific Methods

Viral Infectivity (TLA) Assay

The TLA assay is used to evaluate whether a participant's mucosal levels of infused VRC01 are sufficient to protect the mucosal tissue from *ex-vivo* HIV challenge.

To assess the functionality of infused VRC01 and VRC01LS mAb, rectal tissue explants from female and male participants are challenged *ex vivo* with HIV-1 within 90 minutes of tissue collection. Sections of rectal biopsies are challenged with replication-competent sNLuc.HIV-1_{Bal26}, sNLuc.HIV-$1_{DU422.1}$ and sNLuc.HIV-1_{1086} viral strains containing a secreted nanoluciferase (sNLuc) reporter and expressing the Env ectodomain of HIV-1 Bal26 , Du422.1 or 1086 within an isogenic virus background. To assess the functionality of IV-infused VRC01 and VRC01LS in the female genital tract, cervical and vaginal tissue explants are challenged ex vivo with HIV-1 within 60-120 minutes of tissue collection. Sections of cervical/vaginal biopsy are challenged with sNLuc.HIV-1_{Bal26}. HIV-1 replication in explant cultures is monitored by sNLuc activity (relative light units, RLU) measured every 3 days during days 2-20 post-challenge. Since sNLuc is generated during viral stock preparation, sNLuc activity (RLU) that either increases or plateaus above the limit of detection (two days post-exposure and onwards) indicates productive viral infection.

Susceptibility to viral infection in the *ex vivo* challenge assay will be summarized by the area under the viral infectivity curve (AUC) based on log-transformed RLU values between Days 3-21 (i.e., 2-20 days post-challenge). For samples that do not have Day 21 infectivity measured, their activity will be imputed by the Day 18, Day 20 and Day 22 RLU value. Baseline AUC values will be adjusted for in the assessment of post-baseline AUC values if the Spearman's correlation coefficient assessing the correlation between baseline and post-baseline AUC values is greater than 0.5 with a p-value < 0.05. For comparisons of baseline data between the Seattle and Cape Town sites, RLU values will be performed if systematic differences are observed in standard curves between the Seattle lab and the Cape Town lab (CHIL). Other than AUC, other summary measure of the infectivity curve may be used, including peak RLU or time to reach a certain threshold value of nanoluciferase value.

For each tissue biopsy type, graphical and tabular summaries of the distributions of ex vivo inhibition of HIV-1 infectivity summarized by AUC (or other measurements) will be made for each challenge virus, treatment arm, and timepoint. Comparisons between groups 1-3 will be stratified by site. The difference between treatment arms at a specific timepoint will be tested with an extension of the nonparametric Wilcoxon rank sum test for two-way analysis (i.e., the Van Elteren test) if the data are not normally distributed and with a stratified 2-sample t-test if the data appear to be normally distributed. An appropriate data transformation may be applied to better satisfy assumptions of symmetry and homoscedasticity (constant variance). The same testing

approaches will be used to compare infectivity between male rectal vs. female cervical/vaginal, between male rectal vs. female rectal, and between female cervical vs. female vaginal at each time-point, stratified by dose groups.

ELISA for Hemoglobin

Any secretion sample (semen, PriCol or Softcup) with extrapolated concentrations higher than 10,000 ng/ml are considered blood contaminated and excluded from any statistical analysis. These exclusions are identified by the lab investigator(s).

ELISA for IgG concentration and Quant-iT for Protein concentration

Total protein concentration and total IgG concentration will be used for normalization of VRC01/LS concentrations in serum, secretions and tissues. Total protein and IgG concentrations in study samples will be calibrated via a five-parameter logistic (5PL) model of the standard samples on the same plate. The estimation of the standard curve and the calibration of study samples will be carried out using the nCal package in R (Fong et al., Biometrics, 2012; Fong et al., Bioinformatics, 2013). IgG- and protein-normalizations will be performed by dividing VRC01/VRC01LS levels (pg/mL) by the total IgG and protein concentrations (ng/mL), respectively.

The reported mAb concentrations reflect the measured concentration of mAb in the processed mucosal samples; and the reported values have accounted for the dilution factor in the assay but not the dilution factor due to sample processing and collection, which cannot be determined. Thus, these concentrations cannot be considered physiological concentrations within secretions or tissues.

Singulex assay for mucosal VRC01/VRC01LS Levels

VRC01/LS concentrations will be calibrated via a 5PL model of the standard samples on the same plate. The machine Erenna detects single molecules of VRC01/VRC01LS as photons over a read time. Each measurement of photons above a threshold is considered a detected event and the sum of all photons from these events over the read time (i.e. signal intensity) is called the event photon (EP) measurement for the sample or standard. The EP curve of the VRC01/LS standard will be used to calibrate the VRC01/VRC01LS concentrations in mucosal and serum samples. The lower limit of quantitation (LLoQ) of each run is defined by the lowest standard maintaining less than or equal to 20% coefficient of variation (CV). The estimation of the standard curve and the calibration of study samples will be carried out using the nCal package in R (Fong et al., Biometrics, 2012; Fong et al., Bioinformatics, 2013).

Graphical and tabular summaries of the distributions of VRC01/LS mucosal levels normalized by total IgG/protein, as well as levels data without normalization will be made for each biopsy type, treatment arm, and time point. Correlation plots will be generated between different sample types.

ELISA for VRC01/VRC01LS Levels in Serum

Concentration values below the limit of quantification (=1.0 ug/ml) will be replaced by 0.5 ug/ml in all calculations. Spaghetti plots will be used to display each participant's time-concentration curves, with the treatment group geometric mean or median overlaid. The geometric mean as well as the median and inter-quartile ranges will be used to summarize the drug level at each time-point by treatment group in a summary table.

Individual-level non-compartmental pharmacokinetics (PK) analysis will be performed. Specifically, for Groups 1-3, we will compute drug accumulation based on the ratio of observed trough drug level measurements and the area under the observed time-concentration curve (AUC) for each participant, after the second, third and fourth (Groups 1 & 2 only) infusions as compared to the first. We will report the mean, median, and standard deviation (SD), in addition to the listing of individual values. AUC will be calculated based on raw (not log-transformed) data using the linear trapezoidal method. The actual visit dates will be used in these AUC calculations.

Lastly, for each participant in Groups 1-5, the terminal elimination rate and half-life will be calculated based on the log-linear portion of the time-concentration curve after the last infusion. The terminal rate (slope) will be determined by fitting a linear regression line over the log-transformed concentrations over the actual visit date (in days). The half-life is estimated as log(2) divided by the terminal slope. The effect of participants' characteristics on various PK parameters and inter-individual variabilities of these parameters will be modeled via population compartmental pharmacokinetics analysis and reported separately.

8.6. Analyses prior to end of scheduled follow-up visits

Any analyses conducted prior to the end of the scheduled follow-up visits should not compromise the integrity of the trial in terms of participant retention or safety, drug level or functional endpoint assessments.

8.6.1. Safety

During the course of the trial, analyses of safety data will be prepared approximately every 4 months, as defined in Section 3 of the protocol, for review by the SMB. Ad hoc safety reports may also be prepared for SMB review at the request of the HVTN 116 PSRT. The HVTN leadership must approve any other requests for safety data prior to the end of the scheduled follow-up visits.

8.6.2. Anti-VRC01, anti-VRC0LS and other laboratory assessments

Generally, analysis of a primary laboratory endpoint may be performed when all participants have completed the corresponding visit and data are available for analysis from at least 80% of these participants. The Laboratory Program will review the analysis report prior to distribution to the protocol chairs, DAIDS, vaccine developer, and other key HVTN members and investigators. Distribution of reports will be limited to those with a need to know for the purpose of informing future trial-related decisions.

9. SAFETY TABLES AND FIGURES

9.1 List of Tables

- Enrollment Report
- Demographics and Study Product Administration Frequencies
- Overall Protocol Status
- Maximum Local and Systemic Reactogenicity Summaries
- Adverse Experiences by Body System and Severity – By Decreasing Frequency
- Adverse Experiences by Preferred Term and Severity – By Decreasing Frequency – Includes Severe, Life-threatening or Fatal Events Only
- Adverse Experiences by Preferred Term and Severity – By Decreasing Frequency – Includes Events of All Severities
- Adverse Experiences by Preferred Term and Relationship to Study Product – By Decreasing Frequency – Includes Related Events Only
- Adverse Experiences by Preferred Term and Relationship to Study Product – By Decreasing Frequency – Includes Events of Any Relationship
- Adverse Experiences by Preferred Term and Relationship to Mucosal Sampling – By Decreasing Frequency – Includes Related Events Only
- Adverse Experiences by Preferred Term and Relationship to Mucosal Sampling – By Decreasing Frequency – Includes Events of Any Relationship
- Expedited Adverse Experiences (EAEs) Reported to the Regulatory Support Center (RSC)
- Pregnancy Listing
- Social Impact Summary
- End of Study Diagnostic ELISA Testing Results
- Local Lab Value Summary Statistics

9.2 List of Graphs

- Maximum Local Reactogenicities
- Maximum Systemic Reactogenicities

  Boxplots for Alkaline Phosphatase, AST, ALT, Creatinine, WBC, Hemoglobin, Platelets, Lymphocyte Count, Neutrophil Count

10. ASSAY SPECIFIC TABLES AND FIGURES FOR PROTOCOL TEAM REPORTS

10.1. Viral Infectivity (TLA)

10.1.1. List of Tables

- Summary statistics (i.e., min, mean, median, max, standard deviation) of $AUC_{day3\text{-}21}$ by lab, sex at birth, tissue type, virus, visit, and treatment arm.
- Results of overall comparisons of $AUC_{day3\text{-}21}$ at baseline between FH and CHIL lab using Van Elteren test, stratified by sex at birth, tissue type and virus combination.
- Results of overall comparisons of $AUC_{day3\text{-}21}$ at baseline between female and male rectal samples using Van Elteren test, stratified by site and virus combination.
- Results of comparisons and correlations of $AUC_{day3\text{-}21}$ at baseline between female cervical, vaginal and rectal samples, by lab and virus.
- Results of comparisons of $AUC_{day3\text{-}21}$ between baseline and post-infusion visits, by tissue type, virus, and treatment arm
- Results of comparisons between treatment arms at baseline based on $AUC_{day3\text{-}21}$ and at post-baseline visits based on baseline-subtracted or unsubtracted $AUC_{day3\text{-}21}$, by sex at birth, tissue type, virus, and visit.
- Results of comparisons between tissue types at baseline based on $AUC_{day3\text{-}21}$ and at post-baseline visits based on baseline-subtracted or unsubtracted $AUC_{day3\text{-}21}$.

10.1.2. List of Graphs

- Boxplots of baseline AUC day3-21 by lab, sex at birth, tissue type, and virus, treatment arms combined
- Boxplots of baseline AUC day3-21 by lab, sex at birth, tissue type, virus, visit, and treatment arm
- Lineplots of post-baseline AUC day3-21 by lab, sex at birth, tissue type, and virus, treatment arms combined
- Lineplots of post-baseline AUC day3-21 by lab, sex at birth, tissue type, virus, and treatment arm
- Scatterplots of rectal vs. cervical AUC day3-21 by virus, visit and treatment arm for female participants
- Scatterplot of rectal vs. vaginal AUC day3-21 by virus, visit and treatment arm for female participants
- Scatterplot of cervical vs. vaginal AUC day3-21 by virus, visit and treatment arm for female participants
- Scatterplot of male rectal vs. female rectal AUC day3-21 by virus, visit and treatment arm

10.2. Mucosal VRC01/LS Level

10.2.1. List of Tables

- Summary statistics (i.e., min, mean, median, max, standard deviation, IQR) of VRC01/LS concentration normalized by total IgG and protein, by tissue type, visit, and treatment arm.
- Summary statistics (i.e., min, mean, median, max, standard deviation, IQR) of total IgG and protein, by tissue type, visit, and treatment arm.
- Summary statistics (i.e., min, mean, median, max, standard deviation, IQR) of VRC01/LS concentration without normalization, by tissue type, visit, and treatment arm.

10.2.2. List of Graphs

- Boxplots of baseline mucosal level normalized by total IgG, by sex at birth, tissue type, and treatment arm
- Boxplots of baseline mucosal level normalized by protein, by sex at birth, tissue type, and treatment arm
- Boxplots of baseline mucosal level without normalization, by sex at birth, tissue type, and treatment arm
- Lineplots of baseline and post-infusion mucosal level normalized by total IgG, by sex at birth, tissue type, and treatment arm
- Lineplots of baseline and post-infusion mucosal level normalized by protein, by sex at birth, tissue type, and treatment arm
- Lineplots of baseline and post-infusion mucosal level without normalization, by sex at birth, tissue type, and treatment arm
- Scatterplots of correlation as following:

  Cervicovaginal secretions to Cervical homogenates

  Cervicovaginal secretions to Vaginal homogenates

  Blood to Cervical homogenates

  Blood to Vaginal homogenates

  Blood to Cervicovaginal secretions

  Rectal secretions to rectal homogenates

  Rectal secretions to Semen

  Rectal secretions to blood

  Rectal homogenates to Semen

  Rectal homogenates to blood

  Rectal homogenates to Cervical lysates

  Rectal homogenates to vaginal lysates

Rectal homogenates to cervicovaginal secretions

Rectal secretion to Cervical lysates

Rectal secretion to vaginal lysates

Rectal secretion to cervicovaginal secretions

10.3. Serum VRC01/LS Levels by ELISA

10.3.1. List of Tables

- Summary statistics (i.e., N, N> LLoQ, geometric mean, median, min, max and IQR) of VRC01/LS concentration by visit (number and label), and treatment arm in all participants
- Summary statistics (i.e., N, N> LLoQ, geometric mean, median, min, max and IQR) of VRC01/LS concentration by visit (number and label), and treatment arm among participants who received all infusions
- Summary statistics (N, median and mean +/- SD) of the estimated half-life by treatment group among all participants.
- For Groups 1-3, summary statistics (N, geometric mean, median) of second vs. first, third/first, fourth vs first (if applicable) accumulation in terms of observed trough and observed AUC by treatment group among participants who received all infusions.

10.3.2. List of Graphs

- Individual time-concentration curves with the geometric mean overlaid by treatment group in all participants.
- Individual time-concentration curves with the geometric mean overlaid by treatment group among participants who received all infusions.
- If needed, the above two sets of figures will be repeated with the median (instead of geometric mean) overlaid.

REFERENCES

1. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. Am Stat 1998;52:119-26.

2. Hudgens MG. Estimating cumulative probabilities from incomplete longitudinal binary responses with application to HIV vaccine trials. Statistics in Medicine 2003;22:463-79.

3. Hughes JP. Mixed effects models with censored data with application to HIV RNA levels.Biometrics 1999;55:625-9.

4. Rotnitzky A, Robins J. Analysis of semi-parametric regression models with non-ignorable non-response. Stat Med 1997;16:81-102.

5. Huang Y, Gilbert P, Montefiori D, Self S. Simultaneous evaluation of the magnitude and breadth of a left- and right-censored multivariate response, with application to HIV vaccine development. Statistics in Biopharmaceutical Research 2009;1:81-91.

6. Liu W. On sample size determination of Dunnett's procedure for comparing several treatments with a control. Journal of Statistical Planning and Inference 1997;62:255-61.