



August 29, 2017

Letter of Amendment 1

Version 3.0

HVTN 704/HPTN 085

**A phase 2b study to evaluate the safety and efficacy of
VRC01 broadly neutralizing monoclonal antibody in reducing
acquisition of HIV-1 infection among men and transgender
persons who have sex with men**

DAIDS-ES ID 30095

[IND #113,611—HELD BY DAIDS]

**HIV Vaccine Trials Network (HVTN) Clinical Research Site (CRS) filing
instructions**

The following information impacts the HVTN 704/HPTN 085 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) and any other applicable Regulatory Entity (RE) as soon as possible for their information and review. Their approval is required before implementation.

Upon receiving final IRB/EC and any other applicable Regulatory Entity (RE) approval(s) for this LoA, sites should implement the LoA immediately.

Upon receiving final IRB/EC and any other applicable RE approvals, sites are required to submit a Letter of Amendment (LOA) registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a Registration Notification for the LOA once the DAIDS PRO verifies that all the required LOA registration documents have been received and are complete. A Registration Notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the Registration Notification along with this

letter of amendment and any IRB/EC correspondence should be retained in the site's regulatory files.

For additional information on the registration process and specific documents required for LOA registration, refer to the current version of the DAIDS Protocol Registration Manual.

The following information may also affect the sample informed consent. Your IRB/EC will be responsible for determining the process of informing study participants of the contents of this letter of amendment.

List of changes

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The changes described herein will be incorporated in the next version of Protocol HVTN 704/HPTN 085 if it undergoes full protocol amendment at a later time.

Item 1 Updated in Section 2.9.5, *Particle formation*, and Section 6.2, *Study product formulation*: Product description and formulation/handling instructions

Recent updates to the VRC01 Investigator's Brochure have included revised language describing potential development of white, opaque to translucent particles in vials either before or after thawing and revised handling instructions for the VRC01 vials. Protocol Sections 2.9.5 and 6.2 have been revised accordingly, as shown below (deletions shown by ~~strikethrough~~; added text in **bold underline**).

A Updated in Section 2.9.5, *Particle formation*

Revised:

2.9.5 Particle formation

VRC01 is a highly concentrated protein solution and may develop white, opaque-to-translucent particles after thawing. When particles are observed, they may disappear after a few hours at room temperature or storage at 2°C to 8°C. ~~In previous phase 1 studies, particles have been observed in approximately 1-3% of the vials and generally disappear over a few hours at room temperature. Particle formation upon thawing has no effect on product quality.~~ For additional information, see the IB.

B Updated in Section 6.2, *Study product formulation*

Revised:

6.2 Study product formulation

VRC-HIVMAB060-00-AB [VRC01, Labeled as VRC01 HIV MAb Drug Product VRC-HIVMAB060-00-AB]

VRC01 will be provided as a sterile clear, colorless to yellow isotonic solution, essentially free of visible particles; some opaque or translucent particles may be present. Each vial contains 100 mg / mL of VRC-HIVMAB060-00-AB in formulation buffer. The formulation buffer is composed of 25 mM sodium citrate, 50 mM sodium chloride, and 150 mM L-arginine hydrochloride at pH 5.8. Vials are intended for single use only and do NOT contain a preservative. The product should be stored frozen -35°C to -15°C with excursions permitted between -45°C and -10°C. The study products are described in further detail in the IB.

VRC01 is a highly concentrated protein solution and may develop white, opaque to translucent particles after thawing. When particles are observed, they may disappear after a few hours at room temperature or storage at 2°C to 8°C (36°F to 46°F).

Prior to preparation, vials containing VRC01 must be removed from the freezer and thawed for a minimum of 1 hour at controlled room temperature (maximum 27°C). Following this 1 hour thaw, the unopened vials of VRC01 may be stored for up to 24 hours at controlled room temperature (~~not to exceed~~ maximum 27°C) and/or up to 4 weeks at 2°C to 8°C. Product may NOT be thawed or stored in direct sunlight. Once thawed, product may NOT be refrozen.

Prior to preparation, vials should be swirled for 30 seconds with sufficient force to resuspend any visible particles, yet avoiding foaming. DO NOT SHAKE THE VIALS.

If particles are observed, return the vials to 2°C to 8°C storage.

If the particles re-dissolve within the maximum storage time of up to 4 weeks at 2°C to 8°C, the vials may be used for product preparation. Refrigerated product in the vial must be equilibrated at controlled room temperature (maximum 27°C) for a minimum of 30 minutes before preparation and must be used within 8 hours of removal from the refrigerator.

If particles continue to be observed after 4 weeks at 2°C to 8°C, do not use the vial product for IV bag preparation. These vials must be quarantined until they are returned to the NIAID Clinical Research Products Management Center (CRPMC) or to the manufacturer upon request of the CRPMC or destroyed if directed by the CRPMC.

VRC01 is a highly concentrated protein solution and may develop white to translucent particles after thawing. These particles have been observed in approximately 1-3% of the vials and generally disappear over a few hours at room temperature. Particle formation has no effect on product quality. If the particles do not disappear at room temperature, the vials should be placed in the refrigerator, as particles may continue to dissipate at 2°C to 8°C (36°F to 46°F). Vials that continue to have visible particles after a maximum of 24 hours at controlled room temperature and/or after 4 weeks at 2°C to 8°C (36°F to 46°F) should not be used. Instead, those vials with particles still visible should be quarantined [at 2°C to 8°C (36°F to 46°F)] until they are returned to the NIAID Clinical Research Products Management Center (CRPMC) (or manufacturer upon request of the CRPMC) or destroyed if directed by the CRPMC.

Item 2 Revised in Section 4.9.3, *Monitoring for futility to assess PE*: Futility to assess PE monitoring targets

Recognizing that completion of the AMP trials would be worthwhile if the power to detect the design alternative is greater than 50%, the protocol statisticians have recalculated the second target number of endpoint HIV infections that will be utilized in monitoring for futility to assess PE (prevention efficacy). In addition, the first target number of endpoint infections, which will be used to inform decisions regarding potential enrollment modifications, has been corrected. These revisions to Section 4.9.3 are shown below (deletions shown by ~~striketrough~~; added text in **bold underline**).

Revised:

4.9.3 Monitoring for futility to assess PE

The objective of monitoring the trial for futility to assess PE is to monitor progress toward the minimum needed target number of treatment arm-pooled

HIV-1 primary endpoint infections by the Week 80 visit in the MITT cohort. Two targets are monitored for:

1. the total number of HIV-1 infections needed to achieve the planned 90% power to detect PE = 60%, and
2. the total number of HIV-1 infections needed to achieve ~~65%~~50% power to detect PE = 60%,

each using a 1-sided 0.025-level Wald test of $H_0: PE \leq 0\%$ against $H_1: PE > 0\%$, assuming proportional hazards of HIV-1 infection in the pooled VRC01 and control groups. The target numbers in (1) and (2) are ~~56~~ 57 and ~~29~~ 21, respectively (calculated by solving equation (1) in Schoenfeld [122]. The rationale for considering the two targets is as follows: (i) if the trial cannot achieve the planned 90% power to detect PE = 60%, considerations about enrollment modification or expansion are warranted, and (ii) if the trial cannot achieve even ~~65%~~ 50% power to detect PE = 60%, considerations about completing the trial early for futility to assess PE are warranted.

Two versions of the futility monitoring report will be generated. A report provided to the DSMB will be included in 6-monthly closed DSMB reports, starting in April 2018, and will report:

- a. the estimated distribution of the total (i.e., treatment arm-pooled) number of HIV-1 infections, with corresponding power to reject $H_0: PE \leq 0\%$ using a 1-sided 0.025-level Wald test under the alternative hypothesis PE = 60% throughout the trial,
- b. the estimated probability that the total number of HIV-1 infections is \geq ~~56~~ 57 (target 1) with 95% credible intervals,
- c. the estimated probability that the total number of HIV-1 infections is \geq ~~29~~ 21 (target 2) with 95% credible intervals,
- d. the estimated distribution of the number of HIV-1 infections in each of the three treatment arms.

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 procedure for (a)–(d) will be conducted under each of the following two scenarios:

- the treatment arm-pooled infection rate in (a)–(c) and the three treatment arm-specific infection rates in (d) used for generating future data are based on a Bayesian model and the prior assumption that PE = 60% (the design alternative), and

- the treatment arm-pooled infection rate in (a)–(c) and the three treatment arm-specific infection rates in (d) used for generating future data are based on a Bayesian model and the prior assumption that PE = 0% (the null hypothesis).

The reason for conducting the estimation procedure twice is that the purpose of the results for the ~~56~~ **57** endpoint target (b) is to trigger considerations for trial modifications, whereas the purpose of the results for (c) is to trigger considerations for early trial completion due to futility, where it is desired to reach the guideline (b) more easily/readily than the guideline (c). Accordingly, the results for (b) are interpreted focusing on the prior of PE = 60%, which makes it more likely to reach a guideline than the prior of PE = 0%, and the results for the ~~29~~ **21** endpoint target (c) are interpreted focusing on the prior of PE = 0%, which makes it less likely to reach a guideline than the prior of PE = 60%.

Furthermore, a treatment-blinded report will be generated for distribution to the OC after each DSMB meeting takes place and will report estimates listed in (a)–(c) above calculated based only on treatment-blinded data. The reported results pertaining to estimates (a)–(c) will be identical to those in the DSMB report.

While it is the primary responsibility of the OC 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 OC to complete the trial early due to reaching a guideline for futility to assess PE (specified below).

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

- **[Guideline for enrollment modifications]** If, in the PE = 60% scenario for the prior distribution, the estimated probability of reaching ~~56~~ **57** total infections is less than 25%, the OC may consider enrollment modifications with the intention to be able to conduct the primary PE analysis with adequate power.
- **[Guideline for futility]** If, in the PE = 0% scenario for the prior distribution, the estimated probability of reaching ~~29~~ **21** total infections is less than 25%, the DSMB may recommend completing the trial early based on the inability to conduct the primary PE analysis with adequate power. However, since this is a proof-of-concept trial, a high bar is desired for completing the trial early for futility, and therefore if this event occurs yet the non-efficacy monitoring has not started or the non-efficacy

boundary has not been reached, then this guideline for futility also requires that the estimated PE for the pooled VRC01 vs. control arm is $< 30\%$ and the estimated PE for the VRC01 30 mg/kg vs. control arm is $< 30\%$.

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. In addition, 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, whereas the estimates in (d) will condition on the observed to-date (three) treatment arm-specific HIV-1 incidence rates. All estimates in (a)–(d) will also use the observed to-date treatment arm-pooled dropout rate for generating future dropout data.

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

Item 3 Clarified in Section 5, *Selection and withdrawal of participants:* Eligibility determination

As shown below, text has been added to the final sentence in the first paragraph of Section 5 to clarify that eligibility determination depends on information available to CRS staff at the time of enrollment (added text in **bold underline**).

Revised:

Participants will be healthy, HIV-uninfected (seronegative) adults who comprehend the purpose of the study and have provided written informed consent. Volunteers will be recruited and screened; those determined to be eligible, based on the inclusion and exclusion criteria, will be enrolled in the study. Final eligibility determination will depend on **information available at the time of enrollment**, including results of laboratory tests, medical history, physical examinations, and answers to self-administered and/or interview questions.

Item 4 Updated: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

The Division of AIDS has issued an updated and corrected Version 2.1 of its Table for Grading the Severity of Adult and Pediatric Adverse Events. Accordingly, protocol references to this document have been updated.

A Updated in Section 7.10, *Assessments of reactogenicity*

Revised:

For all participants, baseline assessments are performed before and reactogenicity assessments are performed after infusions per the SSP. All reactogenicity symptoms are graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), **Corrected** Version 2.1, dated ~~March~~ **July** 2017, except as noted in Section 10.2.2.

B Updated in Section 10.2.2, AE reporting

Revised:

An AE is any untoward medical occurrence in a clinical investigation participant administered a study product/procedure(s) and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational study product/procedure(s), whether or not related to the investigational study product/procedure(s). All AEs are graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, **Corrected** Version 2.1, dated ~~March~~ **July** 2017, available on the RSC website at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>, except that the AEs below will be reported according to the SSP:

C Updated in Section 15, Document references (other than literature citations)

Revised:

Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, **Corrected** Version 2.1, dated ~~March~~ **July** 2017. Available at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>

Item 5 Corrected in Appendix D, Tables of procedures (for sample informed consent form): Procedures at week 80 for HIV-uninfected participants

“Interview/Questionnaire”, which was included inadvertently at Week 80 in the Appendix D table of procedures for HIV-uninfected participants, has been removed. This brings the table into alignment with Appendix J, *Schedule I–Procedures at CRS for HIV-uninfected participants*. The corrected Appendix D table is attached.

Item 6 Clarified in Appendices F through I: Assay locations, discard tubes not required, and blood draw totals

A Assay locations clarified

A laboratory at the University of Washington (Seattle, Washington, USA) has been selected to conduct viral isolation/sequencing. This information has been inserted in place of “TBD” in each of the Laboratory procedures appendices. Accordingly, this laboratory has been added to the list of HVTN Laboratories in the footnotes in each appendix and the definition of “TBD” has been removed from footnote 2 in each appendix.

B Discard tubes not required and blood draw totals adjusted

The HVTN Laboratory Program has determined that drawing blood a non-additive discard tube to prevent additive cross-contamination is not needed to ensure the integrity of laboratory assays in this study. Accordingly, the 3mL allowed for this blood draw has been removed from the “Visit total” and “56-Day total” blood draw volumes in Appendices F through I, reverting the Visit and 56-Day blood draw totals to those shown in Version 2.0 of the protocol. The footnote pertaining to use of non-additive discard tubes and the adjustment to blood draw totals has been removed from Appendices F through I.

The revisions to footnotes are shown below (deletions shown by ~~striketrough~~; added text in **bold underline**). The revised appendices, with footnotes modified as shown below, are attached.

Revised in Appendix F:

¹ CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); Peru CTU Laboratory (Lima, Peru); CADIG - Immunodiagnostic Lab (INI-FIOCRUZ) (Rio de Janeiro, Brazil).

² HVTN Laboratories include: Cape Town HVTN Immunology Laboratory (CHIL, Cape Town, South Africa); South African Immunology Laboratory–National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Fred Hutchinson Cancer Research Center (Seattle, Washington, USA); Duke University Medical Center (Durham, North Carolina, USA); University of Cape Town (Cape Town, South Africa); University of Colorado Denver (Aurora, Colorado, USA); **University of Washington (Seattle, Washington, USA)**.

Non-HVTN laboratories: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA); JHU = Johns Hopkins University, HPTN Laboratory Center (Baltimore, Maryland, USA).

~~TBD = Laboratories to be determined by HVTN Laboratory Program.~~

³ Screening may occur over the course of several contacts/visits up to and including day 0 prior to infusion.

⁴ Local labs may assign appropriate alternative tube types for locally performed tests.

⁵ Genotyping may be performed on enrolled participants using cryopreserved PBMC collected at baseline.

⁶ For persons capable of becoming pregnant, pregnancy test must be performed on urine or blood specimens on the day of infusion with negative results received prior to infusion.

⁷ At an early termination visit for a withdrawn or terminated participant (see Section 7.12), blood should be drawn for HIV diagnostic testing, as shown for visit 26 above.

⁸ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

⁹ EDTA blood collected for plasma may also be used for ARV detection assay, if necessary.

¹⁰ Testing plan for ARV detection to be determined.

¹¹ Syphilis testing will be done by serology.

¹² Nucleic acid amplification testing (NAAT) for chlamydia and gonorrhea will be performed on urine and on rectal and oropharyngeal swabs.

¹³ Syphilis testing, and chlamydia/gonorrhea testing by urine and rectal swab, will be performed at visits 2, 9, 15 and 21; in addition, testing may occur at any visit if clinically indicated.

¹⁴ Gonorrhea testing by oropharyngeal swab will be performed at visit 2; in addition, testing may occur at any visit if clinically indicated. A combination gonorrhea/chlamydia oropharyngeal test is allowable (see the SSP for results reporting).

¹⁵ And microscopy if needed.

¹⁶ ~~A 3mL volume is included in the visit totals for drawing a non-additive discard tube to prevent blood tube additive cross-contamination. This is not applicable to the screening visit. Refer to the Specimen Collection SSP for more information.~~

y = SST blood collected for serum storage will also cover specimen needs for the VRC01 drug level, ARV detection, and functional humoral assays; no separate blood draw is needed.

z = ACD blood collected for PBMC storage will also cover specimen needs for host genetics assay; no separate blood draw is needed.

Revised in Appendix G:

- ¹ CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); Peru CTU Laboratory (Lima, Peru); CADIG - Immunodiagnostic Lab (INI-FIOCRUZ) (Rio de Janeiro, Brazil).
- ² HVTN Laboratories include: South African Immunology, Laboratory-National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Duke University Medical Center (Durham, North Carolina, USA); University of Washington (Seattle, Washington, USA).
Non-HVTN laboratories: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA)
~~TBD = Laboratories to be determined by HVTN Laboratory Program.~~
- ³ Local labs may assign appropriate alternative tube types for locally performed tests.
- ⁴ For persons capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.
- ⁵ Visit #.X indicates a Redraw visit where # is a Schedule 1 visit number. Confirmatory draw for HIV diagnostics will be collected at the Redraw visit, in addition to the other indicated specimens. The Redraw visit should occur as soon as possible after the clinic receives a Redraw Request from the HIV diagnostics laboratory. Multiple subsequent Redraw visits may be necessary; only the EDTA blood specimens for HIV diagnostics, viral isolation/sequencing, and plasma storage will be collected at the subsequent Redraw visits. Refer to the HIV Testing SSP for more information.
- ⁶ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.
- ⁷ Date of diagnosis = date of the initial specimen draw that led to the first Redraw Request.
- ⁸ ~~A 3mL volume is included in the visit totals for drawing a non-additive discard tube to prevent blood tube additive cross contamination. Refer to the Specimen Collection SSP for more information.~~

Revised in Appendix H:

- ¹ CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); Peru CTU Laboratory (Lima, Peru); CADIG - Immunodiagnostic Lab (INI-FIOCRUZ) (Rio de Janeiro, Brazil).
- ² HVTN Laboratories include: South African Immunology Laboratory–National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Duke University Medical Center (Durham, North Carolina, USA); University of Colorado Denver (Denver, Colorado, USA); University of Washington (Seattle, Washington, USA).
Non-HVTN laboratories: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA).
~~TBD = Laboratories to be determined by HVTN Laboratory Program.~~
- ³ Local labs may assign appropriate alternative tube types for locally performed tests.
- ⁴ For persons capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.
- ⁵ Visit #.X indicates a Redraw visit where # is a Schedule 1 visit number. Confirmatory draw for HIV diagnostics will be collected at the Redraw visit, in addition to the other indicated specimens. The Redraw visit should occur as soon as possible after the clinic receives a Redraw Request from the HIV diagnostics laboratory. Multiple subsequent Redraw visits may be necessary; only the EDTA blood specimens for HIV diagnostics, viral isolation/sequencing, and plasma storage will be collected at the subsequent Redraw visits. Refer to the HIV Testing SSP for more information.
- ⁶ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.
- ⁷ Date of diagnosis = date of the initial specimen draw that led to the first Redraw Request.
- ⁸ ~~A 3mL volume is included in the visit totals for drawing a non-additive discard tube to prevent blood tube additive cross contamination. Refer to the Specimen Collection SSP for more information.~~

Revised in Appendix I:

- ¹ CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); Peru CTU Laboratory (Lima, Peru); CADIG - Immunodiagnostic Lab (INI-FIOCRUZ) (Rio de Janeiro, Brazil).
- ² HVTN Laboratories include: South African Immunology Laboratory–National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Duke University Medical Center (Durham, North Carolina, USA); University of Colorado Denver (Denver, Colorado, USA); University of Washington (Seattle, Washington, USA).

Non-HVTN laboratories: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA); JHU = Johns Hopkins University, HPTN Laboratory Center (Baltimore, Maryland, USA).

~~TBD = Laboratories to be determined by HVTN Laboratory Program.~~

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ For participants capable of becoming pregnant; pregnancy test may be performed on urine or blood specimens.

⁵ At an early termination visit for a withdrawn or terminated participant (see Section 7.12), blood should be drawn for HIV diagnostic testing, as shown for visit 78 above.

⁶ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

⁷ And microscopy if needed.

⁸ EDTA blood collected for plasma may also be used for ARV detection assay, if necessary.

⁹ Testing plan for ARV detection to be determined.

¹⁰ ~~A 3mL volume is included in the visit totals for drawing a non-additive discard tube to prevent blood tube additive cross-contamination. Refer to the Specimen Collection SSP for more information.~~

y = SST blood collected for serum storage will also cover specimen needs for the VRC01 drug level and functional humoral assays; no separate blood draw is needed.

Item 7 Added in Appendix M, Schedule 4—Procedures at CRS for participants who discontinue infusions for reasons other than HIV infection: Participant unblinding

HVTN studies conventionally include a post-study contact (i.e., following the final scheduled clinic visit) at which study participants are unblinded to their treatment assignments. This contact was inadvertently omitted in Appendix M. That omission has been corrected in the attached revised and corrected Appendix M.

Item 8 Added in Appendix J and M: Post-study confirmation of final HIV test results

For HVTN studies in which diagnostic HIV testing is conducted at the final scheduled study visit, the results of such testing is provided to participants at a contact designated “Post,” at which also the participant is unblinded to his/her treatment assignment. This was inadvertently omitted in the CRS procedure tables for Schedule 1 (Appendix J) and Schedule 4 (Appendix M). This omission has been corrected in the attached revised tables.

Appendix D Tables of procedures (for sample informed consent form)

[Site: You may insert these tables of procedures into appropriate sections of your consent form(s) or give them to study volunteers/participants separately if you think they would be helpful. You are not required to do either.]

HIV-uninfected participants

	<div><div></div><div>6 months</div><div></div><div>1 year</div><div></div><div>1½ years</div><div></div><div>2 years</div><div></div></div>																									
Procedure	Screening visit(s)	First IV visit	4 weeks	8 weeks	8 weeks + 5 days	12 weeks	16 weeks	20 weeks	24 weeks	28 weeks	32 weeks	36 weeks	40 weeks	44 weeks	48 weeks	52 weeks	56 weeks	60 weeks	64 weeks	68 weeks	72 weeks	76 weeks	80 weeks	88 weeks	96 weeks	104 weeks
IV		✓		✓			✓		✓		✓		✓		✓		✓		✓		✓					
Medical history	✓																									
Complete physical exam	✓																									✓
Brief physical exam		✓		✓			✓		✓		✓		✓		✓		✓		✓		✓					
Urine test	✓			✓																					✓	
Blood drawn	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pregnancy test*	✓	✓		✓			✓		✓		✓		✓		✓		✓		✓		✓		✓			
HIV test & pretest counseling	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Risk reduction counseling	✓	✓		✓			✓		✓		✓		✓		✓		✓		✓		✓					✓
Interview/Questionnaire	✓	✓		✓			✓		✓		✓		✓		✓		✓		✓		✓					✓
STI testing (blood, urine, and/or swabs) [†]		✓							✓						✓						✓					

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

* Persons assigned female at birth who have had their uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, are not required to have pregnancy tests.

† And if clinically indicated.

Appendix F Schedule 1—Laboratory procedures for HIV-uninfected participants

Procedure	Ship to ¹	Assay location ²	Tube Type ³	Tube size (vol. capacity) ⁴	Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Total	
					Day:	Screening visit ⁵	D0 W0	D28 W4	D56 W8	D61 W12	D84 W16	D112 W20	D140 W24	D168 W28	D196 W32	D224 W36	D252 W40	D280 W44	D308 W48	D336 W52	D364 W56	D392 W60	D420 W64	D448 W68	D476 W72	D504 W76	D532 W80	D560 W88	D616 W96	D672 W104	D728		
					Week:		Inf#1		Inf#2			Inf#3		Inf#4		Inf#5		Inf#6		Inf#7		Inf#8		Inf#9		Inf#10							
BLOOD COLLECTION																																	
Screening/Diagnostic																																	
Screening HIV test	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5	
HIV diagnostics ⁷	Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	EDTA	10mL	—	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	20 ⁷	260
Safety labs																																	
CBC/ Differential	Local lab	Local lab	EDTA	5mL	5	5	—	5	—	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	55
ALT, Creatinine	Local lab	Local lab	SST	5mL	5	5	—	5	—	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	55
STI Serology																																	
Syphilis ¹¹	Local lab	Local lab	SST	5mL	—	5 ¹³	—	—	—	—	—	—	—	5 ¹³	—	—	—	—	—	5 ¹³	—	—	—	—	—	5 ¹³	—	—	—	—	—	20	
Drug Levels/Detection																																	
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	—	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	0	
ARV detection by serum or plasma ^{8, 10}	CSR	JHU	SST	8.5mL	—	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	0	
ARV detection by dried blood spots ¹⁰	CSR	HVTN Labs	EDTA	2mL	—	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	50
Immunogenicity & Virologic Assays																																	
Host genetics ⁹	CSR	HVTN Labs	ACD	8.5mL	—	z	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0
Anti-VRC01 Ab levels	CSR	VRC / NVITAL	SST	8.5mL	—	y	—	—	—	—	—	—	—	—	—	y	—	—	—	—	—	—	—	—	—	—	y	—	—	—	—	0	
Functional humoral assays ⁸	CSR	HVTN Labs / VRC / NVITAL	SST	8.5mL	—	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	0	
Viral isolation/sequencing ⁹	CSR	HVTN Labs	EDTA	10mL	—	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	250
STORAGE																																	
Serum storage	CSR	—	SST	8.5mL	—	76.5	51	51	42.5	51	42.5	42.5	42.5	42.5	42.5	51	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	51	42.5	42.5	42.5	42.5	1139	
PBMC storage	CSR	—	ACD	8.5mL	—	51	—	—	—	—	—	—	—	—	—	—	34	—	—	—	—	—	—	—	—	—	34	—	—	—	—	153	
Visit total						15	165	73	83	65	73	75	65	80	65	75	73	109	65	80	65	75	65	75	65	114	73	65	65	65	109	1987	
56-Day total						15	180	253	336	221	294	295	212	219	209	219	212	256	246	253	209	219	204	214	204	253	251	251	129	129	173		
URINE COLLECTION																																	
Urine dipstick ¹⁵	Local lab	Local lab			X	—	—	X	—	—	—	—	—	X	—	—	—	—	—	X	—	—	—	—	—	X	—	X	—	—	—		
Pregnancy Test ⁶	Local lab	Local lab			X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—		
Chlamydia/Gonorrhea ¹²	Local lab	Local lab			—	X ¹³	—	—	—	—	—	—	—	X ¹³	—	—	—	—	—	X ¹³	—	—	—	—	—	X ¹³	—	—	—	—	—		
RECTAL SWAB COLLECTION																																	
Chlamydia/Gonorrhea ¹²	Local lab	Local lab			—	X ¹³	—	—	—	—	—	—	—	X ¹³	—	—	—	—	—	X ¹³	—	—	—	—	—	X ¹³	—	—	—	—	—		
OROPHARYNGEAL SWAB COLLECTION																																	
Gonorrhea ¹²	Local lab	Local lab			—	X ¹⁴	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		

¹ CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); Peru CTU Laboratory (Lima, Peru); CADIG - Immunodiagnostic Lab (INI-FIOCRUZ) (Rio de Janeiro, Brazil).

² HVTN Laboratories include: Cape Town HVTN Immunology Laboratory (CHIL, Cape Town, South Africa); South African Immunology Laboratory–National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Fred Hutchinson Cancer Research Center (Seattle, Washington, USA); Duke University Medical Center (Durham, North Carolina, USA); University of Cape Town (Cape Town, South Africa); University of Colorado Denver (Aurora, Colorado, USA); University of Washington (Seattle, Washington, USA).

Non-HVTN laboratories: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA); JHU = Johns Hopkins University, HPTN Laboratory Center (Baltimore, Maryland, USA).

³ Screening may occur over the course of several contacts/visits up to and including day 0 prior to infusion.

⁴ Local labs may assign appropriate alternative tube types for locally performed tests.

⁵ Genotyping may be performed on enrolled participants using cryopreserved PBMC collected at baseline.

⁶ For persons capable of becoming pregnant, pregnancy test must be performed on urine or blood specimens on the day of infusion with negative results received prior to infusion.

⁷ At an early termination visit for a withdrawn or terminated participant (see Section 7.12), blood should be drawn for HIV diagnostic testing, as shown for visit 26 above.

⁸ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

⁹ EDTA blood collected for plasma may also be used for ARV detection assay, if necessary.

¹⁰ Testing plan for ARV detection to be determined.

¹¹ Syphilis testing will be done by serology.

¹² Nucleic acid amplification testing (NAAT) for chlamydia and gonorrhea will be performed on urine and on rectal and oropharyngeal swabs.

¹³ Syphilis testing, and chlamydia/gonorrhea testing by urine and rectal swab, will be performed at visits 2, 9, 15 and 21; in addition, testing may occur at any visit if clinically indicated.

¹⁴ Gonorrhea testing by oropharyngeal swab will be performed at visit 2; in addition, testing may occur at any visit if clinically indicated. A combination gonorrhea/chlamydia oropharyngeal test is allowable (see the SSP for results reporting).

¹⁵ And microscopy if needed.

y = SST blood collected for serum storage will also cover specimen needs for the VRC01 drug level, ARV detection, and functional humoral assays; no separate blood draw is needed.

z = ACD blood collected for PBMC storage will also cover specimen needs for host genetics assay; no separate blood draw is needed.

Appendix G Schedule 2—Laboratory procedures for HIV-1–infected participants

Procedure	Ship to ¹	Assay location ²	Tube Type ³	Tube size (vol. capacity) ³	Visit:	#.X ⁵	Visit:						Total
							31	32	33	34	35		
							D28	D42	D56	D84	D168		
							Weeks after diagnosis ⁷ :	W4	W6	W8	W12	W24	
BLOOD COLLECTION													
Screening or diagnostic assays													
HIV diagnostics	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	EDTA	10mL	20		—	—	—	—	—	20	
HIV PCR viral load	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	EDTA	10mL	—		10	10	10	10	10	50	
CD4+T cell count	Local Lab	Local Lab	EDTA	5mL	5		5	5	5	5	5	30	
Safety lab													
Hemoglobin	Local Lab	Local Lab	EDTA	5mL	—		—	—	5	5	—	10	
Drug levels													
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	8.5		8.5	8.5	8.5	8.5	8.5	51	
Immunogenicity & Virologic Assays													
Functional humoral assays ⁶	CSR	HVTN Labs / VRC / NVITAL	SST	8.5mL	17		17	17	17	17	17	102	
Viral isolation/sequencing	CSR	HVTN Labs	EDTA	10mL	10		10	10	10	10	10	60	
Storage													
Serum	CSR		SST	8.5mL	25.5		17	17	17	17	17	110.5	
Plasma	CSR		EDTA	5mL	5		5	5	5	5	5	30	
PBMC	CSR		ACD	8.5mL	34		—	—	—	34	34	102	
Visit total					125		72.5	72.5	77.5	111.5	106.5	566	
56-Day total					125		198	270	348	334	106.5		
URINE COLLECTION													
Pregnancy Test ⁴	Local Lab	Local Lab			X		—	—	—	X	—		

¹ CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); Peru CTU Laboratory (Lima, Peru); CADIG - Immunodiagnostic Lab (INI-FIOCRUZ) (Rio de Janeiro, Brazil).

² HVTN Laboratories include: South African Immunology, Laboratory-National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Duke University Medical Center (Durham, North Carolina, USA); University of Washington (Seattle, Washington, USA)..

Non-HVTN laboratories: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA)

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ For persons capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

⁵ Visit #.X indicates a Redraw visit where # is a Schedule 1 visit number. Confirmatory draw for HIV diagnostics will be collected at the Redraw visit, in addition to the other indicated specimens. The Redraw visit should occur as soon as possible after the clinic receives a Redraw Request from the HIV diagnostics laboratory. Multiple subsequent Redraw visits may be necessary; only the EDTA blood specimens for HIV diagnostics, viral isolation/sequencing, and plasma storage will be collected at the subsequent Redraw visits. Refer to the HIV Testing SSP for more information.

⁶ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

⁷ Date of diagnosis = date of the initial specimen draw that led to the first Redraw Request.

Appendix H Schedule 3—Laboratory procedures for participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected

Procedure	Ship to ¹	Assay location ²	Tube Type ³	Tube size (vol. capacity) ³	Visit:	#.X ⁵	Visit:			Total
							47	48		
							D28	D168		
							Weeks after diagnosis ⁷ :	W4	W24	
BLOOD COLLECTION										
Screening or diagnostic assays										
HIV diagnostics	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	EDTA	10mL	20		—	—	20	
HIV PCR viral load	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	EDTA	10mL	—		10	10	20	
CD4+T cell count	Local Lab	Local Lab	EDTA	5mL	5		5	5	15	
Drug levels										
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	8.5		—	—	8.5	
Immunogenicity & Virologic Assays										
Functional humoral assays ⁶	CSR	HVTN Labs / VRC / NVITAL	SST	8.5mL	17		—	—	17	
Viral isolation/sequencing	CSR	HVTN Labs	EDTA	10mL	10		—	—	10	
Storage										
Serum	CSR		SST	8.5mL	25.5		17	17	59.5	
Plasma	CSR		EDTA	5mL	5		—	—	5	
PBMC	CSR		ACD	8.5mL	34		—	—	34	
Visit total					125		32	32	189	
56-Day total					125		157	32		
URINE COLLECTION										
Pregnancy Test ⁴	Local Lab	Local Lab			X		—	—		

¹ CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); Peru CTU Laboratory (Lima, Peru); CADIG - Immunodiagnostic Lab (INI-FIOCRUZ) (Rio de Janeiro, Brazil).

² HVTN Laboratories include: South African Immunology Laboratory–National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Duke University Medical Center (Durham, North Carolina, USA); University of Colorado Denver (Denver, Colorado, USA) ; University of Washington (Seattle, Washington, USA)
Non-HVTN laboratories: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA).

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ For persons capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

⁵ Visit #.X indicates a Redraw visit where # is a Schedule 1 visit number. Confirmatory draw for HIV diagnostics will be collected at the Redraw visit, in addition to the other indicated specimens. The Redraw visit should occur as soon as possible after the clinic receives a Redraw Request from the HIV diagnostics laboratory. Multiple subsequent Redraw visits may be necessary; only the EDTA blood specimens for HIV diagnostics, viral isolation/sequencing, and plasma storage will be collected at the subsequent Redraw visits. Refer to the HIV Testing SSP for more information.

⁶ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

⁷ Date of diagnosis = date of the initial specimen draw that led to the first Redraw Request.

Appendix I Schedule 4—Laboratory procedures for participants who discontinue infusions for reasons other than HIV infection

Procedure	Ship to ¹	Assay location ²	Tube Type ³	Tube size (vol. capacity) ³	Visit:	71	72	73	74	75	76	77	78	Total
					Days after enrollment:	D56	D140	D224	D308	D392	D504	D616	D728	
					Weeks after enrollment:	W8	W20	W32	W44	W56	W72	W88	W104	
BLOOD COLLECTION														
Screening or diagnostic assays														
HIV diagnostics ⁵	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	EDTA	10mL	10	10	10	10	10	10	10	10	20 ⁵	90
Safety labs														
CBC/ Differential	Local lab	Local lab	EDTA	5mL	5	—	5	—	5	—	—	—	15	
ALT, Creatinine	Local lab	Local lab	SST	5mL	5	—	5	—	5	—	—	—	15	
Drug Levels/Detection														
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	y	y	y	y	y	y	y	y	0	
ARV detection by serum or plasma ^{8, 9}	CSR	JHU	SST	8.5mL	y	y	y	y	y	y	y	y	0	
ARV detection by dried blood spots ⁹	CSR	HVTN Labs	EDTA	2mL	2	2	2	2	2	2	2	2	16	
Immunogenicity & Virologic Assays														
Functional humoral assays ⁶	CSR	HVTN Labs / VRC / NVITAL	SST	8.5mL	y	y	y	y	y	y	y	y	0	
Viral isolation/sequencing ⁸	CSR	HVTN Labs	EDTA	10mL	10	10	10	10	10	10	10	10	80	
STORAGE														
Serum storage	CSR	—	SST	8.5mL	51	42.5	42.5	42.5	42.5	42.5	42.5	42.5	349	
PBMC storage	CSR	—	ACD	8.5mL	—	—	—	—	—	—	—	34	34	
Visit total					83	65	75	65	75	65	65	109	599	
56-Day total					83	65	75	65	75	65	65	109		
URINE COLLECTION														
Urine dipstick ⁷	Local lab	Local lab			X	—	—	—	—	—	—	X	—	
Pregnancy Test ⁴	Local lab	Local lab			X	—	X	—	X	—	X	—		

¹ CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); Peru CTU Laboratory (Lima, Peru); CADIG - Immunodiagnostic Lab (INI-FIOCRUZ) (Rio de Janeiro, Brazil).

² HVTN Laboratories include: South African Immunology Laboratory–National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Duke University Medical Center (Durham, North Carolina, USA); University of Colorado Denver (Denver, Colorado, USA); University of Washington (Seattle, Washington, USA).

Non-HVTN laboratories: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA); JHU = Johns Hopkins University, HPTN Laboratory Center (Baltimore, Maryland, USA).

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ For participants capable of becoming pregnant; pregnancy test may be performed on urine or blood specimens.

⁵ At an early termination visit for a withdrawn or terminated participant (see Section 7.12), blood should be drawn for HIV diagnostic testing, as shown for visit 78 above.

⁶ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

⁷ And microscopy if needed.

⁸ EDTA blood collected for plasma may also be used for ARV detection assay, if necessary.

⁹ Testing plan for ARV detection to be determined.

y = SST blood collected for serum storage will also cover specimen needs for the VRC01 drug level and functional humoral assays; no separate blood draw is needed.

Appendix J Schedule 1—Procedures at CRS for HIV-uninfected participants

Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Post
Day:	Screening	D0	D28	D56	D61	D84	D112	D140	D168	D196	D224	D252	D280	D308	D336	D364	D392	D420	D448	D476	D504	D532	D560	D616	D672	D728	
Week:	visit ¹	W0	W4	W8		W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W88	W96	W104	
Procedure	Scr.	Inf#1		Inf#2			Inf#3		Inf#4		Inf#5		Inf#6		Inf#7		Inf#8		Inf#9		Inf#10						
Study procedures²																											
Signed screening consent (if used)	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Assessment of understanding	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Signed protocol consent	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Medical history	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Complete physical exam	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—
Abbreviated physical exam	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
Risk reduction counseling	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	X	—
Pregnancy prevention assessment ³	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	X	—
Confirm eligibility, obtain demographics, randomize	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Social impact assessment	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	X	—
Participant Questionnaire	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	X	—
Concomitant medications	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	X	—
Intercurrent illness/adverse experience	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	X	—
HIV infection assessment ⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Confirm HIV test results provided to participant ¹²	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local lab assessment																											
Screening HIV test	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Urine dipstick ¹¹	X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—
Pregnancy (urine or serum HCG) ⁵	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
CBC, differential	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
ALT, Creatinine	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
Syphilis ⁶	—	X ⁷	—	—	—	—	—	—	X ⁷	—	—	—	—	—	X ⁷	—	—	—	—	—	X ⁷	—	—	—	—	—	—
Chlamydia, Gonorrhea ⁸	—	X ⁷	—	—	—	—	—	—	X ⁷	—	—	—	—	—	X ⁷	—	—	—	—	—	X ⁷	—	—	—	—	—	—
Study product administration procedures																											
IV infusion ⁹	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
Reactogenicity assessment ¹⁰	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
Poststudy																											
Unblind participant	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X

¹ Screening may occur over the course of several contacts/visits up to and including day 0 prior to infusion.

² For specimen collection requirements, see Appendix F.

³ Pregnancy prevention assessments are required only for participants who are capable of becoming pregnant.

⁴ Includes pre-test counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant.

⁵ For a participant capable of becoming pregnant, pregnancy test must be performed on the day of infusion prior to infusion. Pregnancy test to determine eligibility may be performed at screening, but must also be done on Day 0 prior to infusion. Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing. Serum pregnancy tests may be used to confirm the results of, or substitute for, a urine pregnancy test.

⁶ Syphilis testing will be done by serology.

⁷ Syphilis and Chlamydia/Gonorrhea testing will be performed at visits 2, 9 15, and 21; in addition, testing may occur at any visit or if clinically indicated.

⁸ Chlamydia/Gonorrhea testing will be done with urine and rectal swabs; oropharyngeal swabs will be collected for gonorrhea testing at visit 2; in addition, testing may occur at any visit if clinically indicated. A combination gonorrhea/chlamydia oropharyngeal test is allowable (see the SSP for results reporting).

⁹ Blood draws required at infusion visits must be performed prior to administration of study product; however, it is not necessary to have results prior to administration, except for results of a serum pregnancy test, if indicated. Lab tests must be drawn within the 3 days prior to infusion.

¹⁰ Reactogenicity assessments performed for 3 days postinfusion (see Section 7.10).

¹¹ And microscopy if needed.

¹² If HIV test results are not available at the visit indicated, provide test results at next available opportunity.

Appendix M Schedule 4—Procedures at CRS for participants who discontinue infusions for reasons other than HIV infection

Visit Number:	71	72	73	74	75	76	77	78	Post
Days after enrollment:	56	140	224	308	392	504	616	728	
Weeks after enrollment:	8	20	32	44	56	72	88	104	
Study procedures¹									
Abbreviated physical exam	X	X	X	X	X	X	X	—	—
Complete physical exam	—	—	—	—	—	—	—	X	—
Risk reduction counseling	X	X	X	X	X	X	X	X	—
Concomitant medications	X	X	X	X	X	X	X	X	—
Intercurrent illness/adverse experience	X	X	X	X	X	X	X	X	—
HIV infection assessment ²	X	X	X	X	X	X	X	X	—
Confirm HIV test results provided to participant ³	X	X	X	X	X	X	X	X	X
Behavioral risk assessment questionnaire	—	X	—	X	—	X	—	X	—
Social impact assessment	X	X	X	X	X	X	X	X	—
Local lab assessment¹									
Urine dipstick ⁴	X	—	—	—	—	—	X	—	—
Pregnancy test ⁵	X	—	X	—	X	—	X	—	—
Poststudy									
Unblind participant	—	—	—	—	—	—	—	—	X

¹ For specimen collection requirements, see Appendix I.

² Includes pre-test counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant.

³ If HIV test results are not available at the visit indicated, provide test results at next available opportunity.

⁴ And microscopy if needed.

⁵ For participants capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

Protocol modification history

Protocol modifications are made to HVTN protocols via clarification memos, letters of amendment, or full protocol amendments. HVTN protocols are modified and distributed according to the standard HVTN procedures as described in the HVTN Manual of Operations (MOP).

The version history of, and modifications to, Protocol HVTN 704/HPTN 085 are described below.

Date: August 29, 2017

Protocol version: Version 3.0

Protocol modification: Letter of Amendment 1

- Item 1 Updated in Section 2.9.5, *Particle formation*, and Section 6.2, *Study product formulation*: Product description and formulation/handling instructions
- Item 2 Revised in Section 4.9.3, *Monitoring for futility to assess PE*: Futility to assess PE monitoring targets
- Item 3 Clarified in Section 5, *Selection and withdrawal of participants*: Eligibility determination
- Item 4 Updated: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events
- Item 5 Corrected in Appendix D, *Tables of procedures (for sample informed consent form)*: Procedures at week 80 for HIV-uninfected participants
- Item 6 Clarified in Appendices F through I: Assay locations, discard tubes not required, and blood draw totals
- Item 7 Added in Appendix M, *Schedule 4—Procedures at CRS for participants who discontinue infusions for reasons other than HIV infection*: Participant unblinding
- Item 8 Added in Appendix J and M: Post-study confirmation of final HIV test results

Date: June 15, 2017

Protocol version: Version 3.0

Protocol modification: Full Protocol Amendment 2

- Item 1 Revised: Study duration and participant follow-up
- Item 2 Updated in Section 1.1: Protocol team membership
- Item 3 Updated in Sections 2.9, 2.9.3, 2.9.4, and Appendix A: VRC01 clinical experience in HVTN 104
- Item 4 Revised in Section 4.9.3: *Monitoring for futility to assess PE*
- Item 5 Clarified in Section 5.1, *Inclusion criteria*: Transgender volunteer eligibility

- Item 6 Added in Section 5.1, *Inclusion criteria*: Hgb criterion adjustment for MTF transgender volunteers using feminizing hormones
- Item 7 Clarified in Section 5.2, *Exclusion criteria*: Tissue or organ transplantation exclusion criterion
- Item 8 Updated in Section 6.2, *Study product formulation*: VRC01 description and storage temperature
- Item 9 Revised in Sections 6.3 and 6.4: Holding times for study products after preparation
- Item 10 Updated in Section 6.4 and Appendix A: Minimum infusion time
- Item 11 Added in Section 6.4, *Administration*: In-line filter set requirement
- Item 12 Clarified in Section 6.4, *Administration*: IV bag temperature equilibration and label weight
- Item 13 Clarified in Section 7.3, *Enrollment and infusion visits*: Timing of HIV infection assessment and HIV testing
- Item 14 Updated in Section 7.10, *Assessments of reactogenicity*, and Section 10.2.2, *AE reporting*: DAIDS AE grading table version and exceptions
- Item 15 Updated in Section 10.2, *Safety reporting*: URLs for referenced documents
- Item 16 Clarified in Section 10.2.2, *AE reporting*: Working hours for CSS or RML response
- Item 17 Updated in Section 10.2.3: *Expedited reporting of adverse events to DAIDS*
- Item 18 Updated in Section 14: Version history
- Item 19 Updated in Section 15, *Document references (other than literature citations)*: Documents and URLs
- Item 20 Corrected in Section 16: *Acronyms and abbreviations*
- Item 21 Corrected in Appendix A, *Sample informed consent form*: Blood draw volumes
- Item 22 Clarified in Appendix A, *Sample informed consent form*: Early termination
- Item 23 Added in Appendix B, *Approved birth control methods for transgender men (for sample informed consent form)*: Condom use and pregnancy testing
- Item 24 Corrected in Appendix D, *Tables of procedures (for sample informed consent form)*: Procedure timepoints
- Item 25 Updated in Appendices F through I: Assay locations, HVTN laboratory listings, and blood draw totals
- Item 26 Revised in Appendices G, H, K, and L: Table format and Schedule 3 blood draws at Visit #.X
- Item 27 Removed in Appendices G and H: Footnote regarding whole blood for HIV diagnostics
- Item 28 Clarified in Appendices J and M: Provision of HIV test results

- Item 29 Added as Appendix N: Protocol signature page
- Item 30 Revised in Letter of Amendment 1 to Version 2.0: Interim safety and feasibility assessments
- Item 31 Corrected: Minor typographical, grammatical, and formatting errors

Date: December 14, 2016

Protocol version: Version 2.0

Protocol modification: Letter of Amendment 1

- Item 1 Revised in Section 1, *Overview* and Section 4.9.1, *Role of the Data Safety Monitoring Board (DSMB)*: Interim safety assessments
- Item 2 Revised in Section 2.4.5, *Trial monitoring*: Feasibility assessment

Date: July 19, 2016

Protocol version: Version 2.0

Protocol modification: Full Protocol Amendment 1

- Item 1 Corrected in Section 1, *Overview*: Estimated total study duration
- Item 2 Added: Switzerland as study location
- Item 3 Added in Section 1 and Appendices F through I: HIV diagnostic laboratories in Peru and Brazil
- Item 4 Updated in Section 1.1: *Protocol team* membership
- Item 5 Revised: PrEP monitoring
- Item 6 Removed in Section 2.9.3, *HVTN 104*: Incorrect systemic reactogenicity rate
- Item 7 Clarified in Sections 4.9.1 and 10.4.3: Data reporting to DSMB
- Item 8 Clarified in Section 4.9.1.1, *Sequential monitoring for potential harm, non-efficacy, and high efficacy*: Caption to Figure 4-6
- Item 9 Added in Section 5.1, *Inclusion criteria*: Reference to SSP for clarification of transgender eligibility
- Item 10 Clarified in Section 5.2, *Exclusion criteria*: PSRT may permit exceptions to Exclusion criterion #4
- Item 11 Clarified in Section 6, *Study product preparation and administration*: Administration volumes, bag covers, and expiration prompts
- Item 12 Removed in Section 7.2, *Pre-enrollment procedures*: Required recording of generic names for concomitant medications
- Item 13 Clarified in Section 7.3, *Enrollment and infusion visits* and Section 7.10, *Assessment of reactogenicity*: Recording and source documentation for reactogenicity events

- Item 14 Clarified in Section 7.3, *Enrollment and infusion visits*, and Appendices D, F, and J: STI testing
- Item 15 Clarified in Section 7.9, *Urine testing*: Follow-up to abnormal urine dipstick result at screening
- Item 16 Clarified in Appendix A, *Sample informed consent form*: VRC01 not being developed for sale
- Item 17 Added in Appendix A, *Sample informed consent form*: Option to include consent for HIV-infected study participants
- Item 18 Renumbered in Appendix A: Section 19, “If you stop getting IVs for reasons other than HIV infection...”
- Item 19 Added in Appendix D: Procedure tables for HIV-infected participants and for participants whose infusions have been stopped for reasons other than HIV infection
- Item 20 Clarified in Appendix E, *Sample consent form for participants with HIV infection at enrollment or during the study*: Number of visits, physical exams, and HIV transmission risk counseling
- Item 21 Throughout protocol document: Minor errors corrected
- Item 22 Updated: Section 14, *Version history*

Date: March 9, 2016

Protocol version: 1.0

Protocol modification: Original protocol

Protocol Signature Page

HVTN 704/HPTN 085

A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection among men and transgender persons who have sex with men

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies

Investigator of Record Name (print)

Investigator of Record Signature

Date

DAIDS Protocol Number: HVTN 704/HPTN 085

DAIDS Protocol Version: Version 3.0

Protocol Date: June 15, 2017