June 15, 2017

Full Protocol Amendment 2

A summary of changes to

Protocol

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.

The HVTN will have operational changes to put in place before the clinical research sites (CRSs) can implement this amendment. Therefore, CRSs may have IRB/EC approval of the amendment but will not be able to implement it until the HVTN completes those changes. The HVTN will send each CRS an amendment activation notification once all the operational changes have been addressed.

By approving this amendment, the IRB/EC approves extending the use of the previous protocol procedures until the CRS receives an amendment activation notification from the HVTN.

Upon receiving final IRB/EC and any other applicable RE approval(s), sites are required to submit an amendment registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a Registration Notification for the amendment once the DAIDS PRO verifies that all the required amendment registration documents have been received and are complete. A Registration Notification from the DAIDS PRO is not required prior to implementing the amendment. A copy of the Registration Notification should be retained in the site's regulatory files.

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

The following information affects the sample informed consent. Your IRB/EC will be responsible for determining the process of informing study participants of the contents of this full protocol amendment.

List of changes

Item 1 Revised: Study duration and participant follow-up

Pharmacokinetic data from the HVTN 104 phase 1 trial of the VRC01 monoclonal antibody indicates that complete systemic clearance of the study product takes longer than previously believed. For this reason, follow-up has been extended to 32 weeks following the final study product administration, increasing the study duration per participant from 92 to 104 weeks. This change has been propagated through multiple protocol sections as shown below.

A Revised in Section 1, *Overview*

In Section 1, the final visit in Table 1-1, *Schema*, has been changed to Week 104 and the associated footnote now indicates that Week 104 is the last study visit for endpoint analysis of safety and tolerability. In addition, the Duration per participant has been revised from 21 to 24 months and estimated total study duration has been revised from 59 to 62 months.

B Revised in Section 2.4.2, *Dose and schedule*

The second paragraph in Section 2.4.2 has been revised to indicate that follow-up will continue for 24 weeks following the final primary follow-up visit at Week 80 and that the total study duration for each participant is 104 weeks (2 years) rather than 92 weeks (approximately 1.75 years).

C Revised in Section 4.6.1, *Assumptions of the sample size calculations including sequential monitoring for PE*

The third bullet in Section 4.6.1 has been revised to assume that visits continue every 4 weeks through Week 80 and HIV-1 status at Week 80 is known.

D Revised in Section 4.13.7.1, *Sampling of mAb markers*

The first paragraph in Section 4.13.7.1 has been revised to indicate that mAb group control participants will represent a random sample of those who complete follow-up to the Week 96 visit HIV-1 negative. The second bullet in this section has been revised to indicate that mAb group and control group marker subset controls will have marker measurements every 4 weeks through Week 80, plus Day 61 and Weeks 88 and 96. The final sentence in this section has been revised to indicate that samples drawn every 4 weeks through Week 80, plus samples drawn at Weeks 88 and 96, provide the basis for modeling marker curves over time. This allows samples drawn up to 24 weeks post the last infusion to be included in the model.

E Revised in Appendix A, *Sample informed consent form*

Section 8 in the *Sample informed consent form* has been revised to indicate that a participant's visits will be scheduled over about 2 years and that after the first 1½ years, visits will be about 8 weeks apart.

Section 19 has been revised to indicate that study visits for participants who stop getting IVs for reasons other than HIV infection will occur every 3 to 4 months until 104 weeks (2 years) after the first infusion.

F Revised in Appendix B, Approved birth control methods for transgender men (for sample informed consent form

The timing of the last scheduled clinic visit has been revised in the second paragraph in Appendix B.

G Visit schedule revised in Appendix D: *Tables of procedures (for sample informed consent form)*

The visit schedules in Appendix D for *HIV-uninfected participants* and for *Participants who discontinue infusions for reasons other than HIV infection* have been revised to show follow-up to Week 104. Study procedures for the final three visits in each schedule remain unchanged, except as indicated in Item 24.

H Visit schedule revised in Appendices F and J: Schedule 1 laboratory and CRS procedures for HIV-uninfected participants

Timepoints for the final two visits in Schedule 1 have been revised to extend follow-up to 104 weeks after enrollment.

I Visit schedule revised in Appendices I and M: Schedule 4 laboratory and CRS procedures for participants who discontinue infusions for reasons other than HIV infection

Timepoints for Visits 76 through 78 have been revised in these appendices.

Item 2 Updated in Section 1.1: Protocol team membership

The protocol team list in Section 1.1 has been updated.

Item 3 Updated in Sections 2.9, 2.9.3, 2.9.4, and Appendix A: VRC01 clinical experience in HVTN 104

The number of clinical trial recipients who have received VRC01 has been updated in Section 2.9 and Section 3 of Appendix A, *Sample informed consent form*. In addition, the safety experience summaries in Section 2.9.3, *HVTN 104*, and Section 2.9.4, *Safety summary of VRC01*, have been updated per the final unblinded HVTN 104 safety report. The number of VRC01 clinical trials, total number of participants in those trials, and approximate number of VRC01 recipients have been updated under "Risks of VRC01 antibody) in Section 3 of Appendix A, *Sample informed consent form*. In addition, the second paragraph in this section has been updated with post-unblinding information from the HVTN 104 trial.

Item 4 Revised in Section 4.9.3: *Monitoring for futility to assess PE*

Section 4.9.3 has been rewritten to describe a revised monitoring plan to assess PE. The revised plan facilitates futility assessment by the DSMB and provides better guidance to decisions concerning trial conduct, taking into account the trial's proof-of-concept design. The revised language also reflects requests from the DSMB, expressed at a meeting held April 26, 2017, regarding the scope of interim futility analyses. The revised plan focuses on estimating the distribution of the number of HIV-1 infection endpoints by Week 80 rather than (previously) on the distribution of time to a prespecified number of endpoints. Futility guidelines are defined in terms of probabilities of reaching prespecified targets for the number of endpoint infections. Targets monitored for include inability to achieve the planned 90% power and inability to achieve 65% power for PE = 60%. Estimation procedures are conducted under two distinct assumptions about PE in the yet-to-be-observed portion of the data in order to facilitate considerations for trial modifications and early trial completion.

Item 5 Clarified in Section 5.1, *Inclusion criteria*: Transgender volunteer eligibility

In order to eliminate potential confusion regarding whether HIV risk criteria apply to transgender volunteers, notation that both male-to-female and female-to-male transgender volunteers are eligible has been moved to parentheses prior to the bullets specifying the HIV risk criteria.

Item 6 Added in Section 5.1, *Inclusion criteria*: Hgb criterion adjustment for MTF transgender volunteers using feminizing hormones

In recognition that lab normal values for some hematologic parameters may differ for transgender persons who were born male but who are taking feminizing hormones, such as anti-androgens or estrogens, Inclusion criterion #10 has been revised to set a minimum hemoglobin value of 12.0 g/dL for such persons.

Item 7 Clarified in Section 5.2, *Exclusion criteria*: Tissue or organ transplantation exclusion criterion

Exclusion criterion #17 has been revised to clarify that the intent is to exclude volunteers who have received the sort of organ or tissue transplant typically accompanied by immunosuppressive medications, which does not include reconstructive orthopedic, ENT, or cosmetic surgery.

Item 8 Updated in Section 6.2, *Study product formulation*: VRC01 description and storage temperature

Per the updated Investigator's Brochure, the first sentence in Section 6.2 has been revised to indicate that VRC01 in the vial is clear and colorless and essentially free of visible particles, though some opaque or translucent particles may be present. In the same paragraph, language describing the storage temperature for VRC01 has been revised, per the Investigator's Brochure, to specify storage at -35°C to -15°C with excursions permitted between -45°C and -10°C.

Item 9 Revised in Sections 6.3 and 6.4: Holding times for study products after preparation

The "in use" hold times and maximum controlled room temperatures for the intravenous administration of the VRC01 drug product have revised in the Investigator's Brochure. The study product preparation and administration sections of protocol HVTN 704/HPTN 085 have been updated accordingly. In addition, for consistency with instructions in Section 6.2, clarification has been added in Sections 6.3.1 and 6.3.2 that the product should not be used if "**visible** particles are present."

Item 10 Updated in Section 6.4 and Appendix A: Minimum infusion time

Per an update to the VRC01 Investigator's Brochure, VRC01 infusions may be administered over as little as 15 minutes. The final paragraph in Section 6.4 has been revised accordingly. This change has also been made in Section 8 of Appendix A, *Sample informed consent form*.

Item 11 Added in Section 6.4, *Administration*: In-line filter set requirement

On the recommendation of the US FDA, the VRC01 Investigator's Brochure was revised to require use of in-line filter sets for all IV administrations of the VRC01 study product. Section 6.4, *Administration*, has been updated accordingly.

Item 12 Clarified in Section 6.4, *Administration*: IV bag temperature equilibration and label weight

The first paragraph in Section 6.4 has been revised to clarify that, if an IV bag has been stored at 2–8°C, it must be equilibrated to room temperature for 30 minutes or longer. The second paragraph has been revised to clarify that IV bags may be administered if participant weight used to prepare the IV bag (which is recorded on the IV bag label) is within 10% of the participant's current actual weight.

Item 13 Clarified in Section 7.3, *Enrollment and infusion visits*: Timing of HIV infection assessment and HIV testing

While blood collection for HIV diagnostic testing must be completed prior to infusions at infusion visits (as specified in Section 7.3), there is no need for the activities associated with *HIV infection assessment*, including *pre-test counseling*, to be completed at that time. Accordingly, *HIV infection assessment* has been moved to the list of procedures performed at all infusion visits but that may be performed prior to, during, or following infusion.

Item 14 Updated in Section 7.10, *Assessments of reactogenicity*, and Section 10.2.2, *AE reporting*: DAIDS AE grading table version and exceptions

In Section 7.10, *Assessments of reactogenicity*, and Section 10.2.2, *AE reporting*, the *Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events* has been updated to Version 2.1, dated March 2017. The list of exceptions to the grading table in Section 10.2.2 has been revised for alignment with the new version of the grading table. Specifically, the first bullet in the list has been revised to specify "Unintentional weight loss…" and the bullet for insomnia have been removed. A bullet has been added to the list of exceptions for "Infusion reactions". In addition, language clarifying hemoglobin AE grading for transgender participants on feminizing or masculinizing hormone therapy has been added.

Item 15 Updated in Section 10.2, *Safety reporting*: URLs for referenced documents

URLs for DAIDS documents referenced in Sections 10.2.2 and 10.2.3 have been updated.

Item 16 Clarified in Section 10.2.2, *AE reporting*: Working hours for CSS or RML response

Per the addition of a Regional Medical Liaison for South America, who may respond to emailed AE notifications, Peru Time has been added to the list of the relevant time zones for "working hours."

Item 17 Updated in Section 10.2.3: *Expedited reporting of adverse events to DAIDS*

Text in Section 10.2.3 describing expedited reporting of adverse events to DAIDS has been updated to conform to current DAIDS and HVTN protocol template language.

Item 18 Updated in Section 14: Version history

The version history has been corrected and updated in Section 14 of the protocol.

Item 19 Updated in Section 15, *Document references (other than literature citations)*: Documents and URLs

Documents not referenced elsewhere in the protocol have been removed from the list in Section 15. Document versions and URLs for Division of AIDS documents have been updated as appropriate. Notice has been added that the HVTN Lab Assay Algorithm is available upon request.

Item 20 Corrected in Section 16: *Acronyms and abbreviations*

Acronyms and abbreviations that either do not appear elsewhere in the protocol or that appear only once and are fully defined in that location have been removed from the list in Section 16. Following HVTN convention, several acronyms have been defined at first use in the protocol.

Item 21 Corrected in Appendix A, *Sample informed consent form*: Blood draw volumes

The minimum and maximum blood draw volumes indicated in the first full paragraph in Section 12 of the *Sample informed consent form* have been corrected to conform to the minimum and maximum volumes specified in Appendices F through I. The maximum figure in the consent form includes a customary overage to allow redraws for safety labs if these are needed.

Item 22 Clarified in Appendix A, *Sample informed consent form*: Early termination

Text in Sections 19, 20, and 26 in Appendix A has been revised to clarify procedures for participants terminated from the study before completing the schedule of clinic visits. Specifically, the topic sentence in Section 19 has been revised to indicate that participants who stop getting IVs for reasons other than HIV infection may, rather than will, be encouraged to stay in the study. The topic sentence in Section 20 has been revised to indicate that this consent section applies specifically to participants terminated for cause. A bullet indicating that enrollment in error (eg, learning that an enrolled participant did not meet all eligibility criteria) is cause for termination has been added along with text indicating that terminated participants will be asked to complete a final clinic visit that includes a physical exam, possible blood draws and urine sampling, and collection of social impact data. Finally, the first sentence in the second paragraph in Section 26 has been revised to clarify that this paragraph applies specifically to participants who decide of their own volition to leave the study early.

Item 23 Added in Appendix B, *Approved birth control methods for transgender men (for sample informed consent form)*: Condom use and pregnancy testing

Two sentences advising the use of condoms to prevent HIV infection and advising that pregnancy testing will be conducted have been added at the end of Appendix B.

Item 24 Corrected in Appendix D, *Tables of procedures (for sample informed consent form)*: Procedure timepoints

For consistency with the laboratory and clinic procedures tables, Appendices F through M, tables in Appendix D have been corrected to indicate that:

- Risk reduction counseling will not be performed at the Week 80 visit in Schedule 1 for HIV-uninfected participants
- Pregnancy testing will be performed only at Weeks 8, 32, 56, and 88 in Schedule 4 for participants who discontinue infusions for reasons other than HIV infection
- Urine testing will be performed at Weeks 8 and 88 in Schedule 4.

Item 25 Updated in Appendices F through I: Assay locations, HVTN laboratory listings, and blood draw totals

Per an update in the HVTN Laboratory Program conventions for listing endpoint labs, in Appendix F, *Schedule 1—Laboratory procedures for HIV-uninfected participants*, the assay locations for "ARV detection by dried blood spots" and for "Host genetics" have been changed from "UC Denver" and "FHCRC" to "HVTN Labs." Similarly, "Duke/SAIL-NICD" has been replaced with "HVTN Labs" as the assay location for "Functional humoral assays" in Appendices F through I. In addition, footnotes 1 and 2 to each table have been revised to list all labs performing HIV diagnostic testing under footnote 1, to list all labs with HVTN funding to perform their protocol-designated endpoint assays under "HVTN Laboratories" in footnote 2 and listing only those labs that do not receive such funding as "Non-HVTN laboratories."

Visit and 56-day total blood draw volumes have been adjusted in each appendix to account for drawing a 3mL non-additive discard tube at each visit. This is required to prevent blood tube additive cross contamination. A footnote has been added to each table referencing the Specimen Collection SSP for additional information.

Item 26 Revised in Appendices G, H, K, and L: Table format and Schedule 3 blood draws at Visit #.X

The tables in Appendices G, H, K, and L have been reformatted to clarify the purpose of the visit denoted "#.X" and to clarify that the date of diagnosis, which can only be known upon completion of confirmatory HIV testing, is the date on which the initial specimen was drawn that led to the first redraw request for confirmatory HIV testing. Footnotes have been added to clarify these points for CRS staff.

In addition, because CRS staff cannot know whether at the time of Visit #.X whether a participant will ultimately be assigned to Schedule 2 (for HIV-1–infected participants) or to Schedule 3 (for those discovered to have been infected at enrollment or who become HIV-1–infected), blood draws at Visit #.X have been harmonized across the two schedules.

Item 27 Removed in Appendices G and H: Footnote regarding whole blood for HIV diagnostics

Former footnote #7 in Appendix G and footnote #5 in Appendix H, regarding shipment of one tube of unprocessed whole blood to the HIV diagnostics laboratory, has been removed from the protocol. This instruction is included in site processing lab instructions.

Item 28 Clarified in Appendices J and M: Provision of HIV test results

The purpose of the "Confirm HIV test results provided to participant" procedure is to prevent unnecessary delay in provision of HIV test results to study participants. Since it is not possible for those results to be given to participants until the CRS receives them from the HIV diagnostic laboratory, a clarifying footnote has been added to this row in the Appendix J and Appendix M procedures tables.

Item 29 Added as Appendix N: Protocol signature page

Per Division of AIDS policy for new protocol versions and letters of amendment, a protocol signature page has been added to the protocol document as Appendix N.

Item 30 Revised in Letter of Amendment 1 to Version 2.0: Interim safety and feasibility assessments

Restrictions on enrollment prior to completion of an interim safety assessment and an operational feasibility assessment were removed.

A Revised in Section 1, *Overview*

The paragraph immediately below Table 1-1 was revised to remove the enrollment restriction prior to completion of the interim safety assessment and an earlier review of interim safety data requested by the US FDA was added.

B Revised in Section 4.9.1, *Role of the Data Safety Monitoring Board (DSMB)*

The final paragraph in Section 4.9.1, describing the interim safety assessment and enrollment restriction was removed.

C Revised in Section 2.4.5, *Trial monitoring*: Feasibility assessment

The final clause in the first paragraph in Section 2.4.5, which restricted enrollment prior to completion of a feasibility assessment, was removed.

Item 31 Corrected: Minor typographical, grammatical, and formatting errors

Minor typographical, grammatical, and formatting errors have been corrected throughout the protocol document.

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: 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: NA (Original protocol)