March 7, 2018

Letter of Amendment 2

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]

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 affects 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

Item 1 Corrected in Sections 6.3.1 and 6.3.3: IV bag/glass bottle labeling instructions 2

Item 2 Added in Appendices A and C: Broad regulatory agency access to participant study records 3

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 Corrected in Sections 6.3.1 and 6.3.3: IV bag/glass bottle labeling instructions

Changes to the IV bag/glass bottle labeling instructions instituted in Clarification Memo 1 to protocol Version 3.0 were applied inconsistently across the study arms, thus threatening to unblind treatment assignments for some study participants. In addition, the revised labeling was inconsistent with information in the current Investigator's Brochure. For these reasons, the labeling instructions in Sections 6.3.1 and 6.3.3 of protocol Version 3.0 have been restored, as shown below (deletion shown by ~~strikethrough~~; added text in **<u>bold underline</u>**).

A Corrected in Section 6.3.1, *VRC-HIVMAB060-00-AB (10mg/kg IV) - (Group 1)*

…The IV bag or IV glass bottle will be labeled with a DO NOT INFUSE after date and time as follows:

- 24 hours if stored at 2°C to 8°C
- 8 hours, including completion of infusion, if stored at controlled room temperature (**<u>not to exceed 30°C</u>** ~~maximum 27°C~~)

Product may NOT be stored in direct sunlight.

…

B Corrected in Section 6.3.3, *Control for VRC01 (Group 3)*

… The IV bag or IV glass bottle will be labeled with a DO NOT INFUSE after date and time as follows:

- 24 hours if stored at 2°C to 8°C
- 8 hours, including completion of infusion, if stored at controlled room temperature (**not to exceed 30°C** ~~maximum 27°C~~)

Product may NOT be stored in direct sunlight.

Item 2 Added in Appendices A and C: Broad regulatory agency access to participant study records

For consistency with ICH E6 (R2) 4.8.10(n), notation has been added to Appendix A, *Sample informed consent form* (Items 14 and 22), and Appendix C, *Sample consent form for use of samples and information in other studies* (Item 11), that any regulatory agency that reviews clinical trials may have access to participant study records (added text in **bold underline**).

A Revised in Appendix A, Item 14

People who may see your information are:

- Researchers who use your stored samples and limited information for other research
- Government agencies that fund or monitor the research using your samples or information
- **Any regulatory agency that reviews clinical trials**
- The researcher's Institutional Review Board or Ethics Committee
- The people who work with the researcher

All of these people will do their best to protect your information. The results of any new studies that use your extra samples or information may be published. No publication will use your name or identify you personally.

B Revised in Appendix A, Item 22

Clinic staff will have access to your study records. Your records may also be reviewed by groups who watch over this study to see that we are protecting your rights, keeping you safe, and following the study plan. These groups include:

- The US National Institutes of Health, people who work for them, its study monitors, and its chosen South African representatives,

- The US Food and Drug Administration,
- **Any regulatory agency that reviews clinical trials,**
- [Insert name of local IRB/EC] ,
- [Insert name of local and/or national regulatory authority as appropriate],
- The HVTN and HPTN and people who work for them,
- The US National Institutes for Allergy and Infectious Diseases Data and Safety Monitoring Board, and
- The US Office for Human Research Protections.

All reviewers will take steps to keep your records private.

C Revised in Appendix C, Item 11

People who may see your information are:

- Researchers who use your stored samples and limited information for other research
- Government agencies that fund or monitor the research using your samples or information
- **Any regulatory agency that reviews clinical trials**
- The researcher's Institutional Review Board or Ethics Committee
- The people who work with the researcher

All of these people will do their best to protect your information. The results of any new studies that use your extra samples or information may be published. No publication will use your name or identify you personally.

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: March 7, 2018

Protocol version: Version 3.0
Protocol modification: Letter of Amendment 2

Item 1 Corrected in Sections 6.3.1 and 6.3.3: IV bag/glass bottle labeling instructions

Item 2 Added in Appendices A and C: Broad regulatory agency access to participant study records

Date: November 9, 2017

Protocol version: Version 3.0
Protocol modification: Clarification Memo 1

Item 1 Clarified in Section 6, *Study product preparation and administration*: Sodium Chloride for Injection USP, 0.9% containers and volumes

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: Version 1.0
Protocol modification: Original protocol

Protocol Signature Page

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