August 25, 2017

Full Protocol Amendment 2

A summary of changes to

Protocol

Version 3.0

HVTN 703/HPTN 081

A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection in women in sub-Saharan Africa

DAIDS-ES ID 12045

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

The following information impacts the HVTN 703/HPTN 081 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 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 indicate 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, *Duration per participant* has been revised from 21 to 24 months and *Estimated total study duration* has been revised from 57 to 60 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 4.4.1, *Assumptions of the sample size calculations including sequential monitoring for PE*

The third bullet in Section 4.4.1 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 4.11.7.1, *Sampling of mAb markers*

The first paragraph in Section 4.11.7.1 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 2 months 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 sample informed consent form)*

The period for which effective birth control is required has been revised in the second paragraph of 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.

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

Timepoints for the final three 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 Revised in Section 2.4.5, *Trial monitoring*: Feasibility assessment

For consistency with sister protocol HVTN 704/HPTN 085 and given ongoing monitoring of feasibility parameters along with DSMB review of these parameters and recommendation that enrollment should continue, the phrase conditioning continued enrollment on completion of a formal feasibility assessment has been removed at the end of the first paragraph in Section 2.4.5.

Item 4 Updated in Sections 2.9, 2.9.3, 2.9.4, 2.10, and Appendix A: VRC01 clinical experience in HVTN 104

The number of clinical trial recipients who have received VRC01 has been updated in the first paragraph of Section 2.9 and in Section 3 of Appendix A, *Sample informed consent form*. Since many of these recipients have been in other than phase 1 trials, "Phase 1" has been removed from the section title. 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. The final bullet describing severe systemic reactogenicity symptoms in VRC01 recipients in HVTN 104 has been revised to clarify that grade 1 headache occurred on Day 1. In addition, the first sentence in the second paragraph of Section 2.10, *Potential risks of study products and administration*, has been revised for clarity and a cross-reference to Section 2.9.4, *Safety summary of VRC01*, has been added.

Item 5 Updated in Section 2.9.5, *Particle formation*, and Section 6.2, *Study product formulation*: Product description and formulation/preparation instructions

A Updated in Section 2.9.5, *Particle formation*

For consistency with the updated Investigator's Brochure, Section 2.9.5 has been revised to indicate that white, opaque to translucent particles may develop after thawing and that these particles may disappear after a few hours. Estimates of the frequency of such particles and their lack of effect on product quality have been removed.

B Updated in Section 6.2, *Study product formulation*

With respect to potential development of white, opaque to translucent particles either before or after thawing, the description of VRC01 and handling instructions for

VRC01 vials have been revised for consistency with the updated Investigator's Brochure.

Item 6 Revised in Section 4.7.3: *Monitoring for futility to assess PE*

Section 4.7.3 has been rewritten to describe a revised monitoring plan to assess prevention efficacy (PE). The revised plan facilitates futility assessment by the DSMB and provides better guidance for 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 50% 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. Specific guidelines for enrollment modification and for futility have been added.

Item 7 Clarified in Section 5: Eligibility determination

Text has been added to the final sentence in the first paragraph of Section 5 to clarify that eligibility determination depends on information available at the time of enrollment.

Item 8 Clarified in Section 5.2, *Exclusion criteria*: Tissue or organ transplantation exclusion criterion

Exclusion criterion #17 has been revised to clarify that the intended exclusion is specific to receipt of organ/tissue transplantation typically accompanied by immunosuppressive medications, which does not apply to reconstructive orthopedic, ENT, or cosmetic surgery.

Item 9 Clarified in Section 6.4, *Administration*: IV bag label weight and IV tubing flushing

The second paragraph in Section 6.4 has been revised to clarify that IV bags may be administered if the 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 10 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 11 Updated in Section 7.10, *Assessments of reactogenicity*, Section 10.2.2, *AE reporting*, and Section 15, *Document references (other than literature citations)*: DAIDS AE grading table version and exceptions

References to the DAIDS AE grading table have been updated to reflect promulgation of "Corrected" Version 2.1, dated July 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".

Item 12 Updated in Sections 10.2: URLs for referenced documents

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

Item 13 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 with current DAIDS and HVTN protocol template language.

Item 14 Updated in Section 14: *Version history*

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

Item 15 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 16 Updated 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 addition, an acronym newly added in Section 1.1 has been added to the list.

Item 17 Updated in Appendix A, *Sample informed consent form*: Minimum infusion time

Per the revised VRC01 Investigator's Brochure and consistent with changes in protocol Section 6.4 (see Item 27C), Section 8 of Appendix A has been updated to indicate that the IV infusion procedure typically takes about 15 minutes to an hour.

Item 18 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 19 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. Accordingly, the final sentence in this section, indicating that such participants may be asked to stay in the study, has been removed. 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 20 Revised in Appendix B, *Approved birth control methods (for sample informed consent form)*: Approved contraception methods

A Barrier contraception requirement removed

In the Standard Treatment Guidelines and Essential Medicines List for South Africa (Section 7.3), use of condoms is indicated primarily to prevent HIV and STI transmission/acquisition. All clinical sites in this study provide condoms free of charge for this purpose. In addition, frequent scheduled HIV risk reduction counseling includes discussion of condom use, especially in light of the potential for increased likelihood of HIV acquisition associated with use of injectable hormonal contraceptives. Furthermore, the following caution has been added at the end of

Appendix B, "Remember: If you are having sex, you need to use male or female condoms to protect yourself from HIV infection." In this context, because addition of a barrier method does not appreciably improve contraceptive efficacy, because participants may not have the capacity to negotiate condom use on a regular basis, and because making this a required element of effective contraception imposes an unreasonable burden on prospective study participants, one to which they are unlikely to adhere for the duration of the clinical trial, barrier contraception requirement has been removed from the list of effective birth control methods in Appendix B.

B Partner vasectomy removed as contraception method

Inclusion of successful vasectomy in the male partner as a method of effective contraception is inappropriate in a study including females at significant risk for HIV infection as such persons are unlikely to have only one male partner and may change partners often, in which case vasectomy in any particular partner will not constitute effective contraception. In addition, it would be extremely difficult for a participant who otherwise qualifies for enrollment to have only male partners who have had vasectomies throughout the duration of the trial. For these reasons, this provision has been removed from Appendix B.

C Notice of pregnancy tested added

Per recent revision to the HVTN protocol template, a sentence advising that pregnancy testing will be performed has been added at the end of Appendix B.

Item 21 Corrected in Appendix D, *Tables of procedures (for sample informed consent form)*: Procedure timepoint

For consistency with the laboratory and clinic procedures tables, the procedure table for *HIV-uninfected participants* in Appendix D has been corrected to indicate that "Risk reduction counseling" and "Interview/questionnaire" will not be performed at the Week 80 visit.

Item 22 Clarified in Appendix F: DBS allowance applies to Visit and 56-day blood draw totals

In order to clarify that 2mL for possible dried blood spot acquisition (per footnote 16) has been added to blood draws specified for all clinic visits for HIV-uninfected participants, footnote 17 has been applied to "Visit total" as well as to "56-day total".

Item 23 Updated in Appendices F through I: Assay locations and HVTN laboratory listings

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" and "HVTN Labs" has replaced "TBD" as the assay location for viral isolation and sequencing 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 protocol-designated endpoint assays under "HVTN Laboratories" in footnote 2 and listing only labs that do not receive such funding as "Non-HVTN laboratories." As the University of Cape Town has been selected to conduct viral isolation and sequencing, this laboratory has been added to the footnote 2 list of "HVTN Labs" in Appendices G, H, and I. As "TBD" no longer appears in the procedures tables, definition of "TBD" has been removed from footnote 2 in Appendices F through I. Finally, in Schedules 1 and 4 (Appendix F and Appendix I, respectively), UW-VSL has been added as a "Ship to" location for HIV diagnostics (note that it was already in place as an "Assay location" for this assay in these appendices); accordingly, UW-VSL has been added to footnote 1 in Appendix F and in Appendix I.

Item 24 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 25 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. In addition, confirmation that HIV test results have been provided has been added to the column for a post-study contact in Appendix J and to a new post-study column in Appendix M. In addition, new rows for Poststudy unblinding of the participant to his/her treatment assignment have been added to Appendix M.

Item 26 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 27 Updated in Sections 6.2 through 6.4 per Clarification Memo 1 to protocol Version 2.0: Study product description, storage, and administration instructions

Clarification Memo 1 to protocol Version 2.0 revised protocol sections concerning study product formulation, preparation, and administration based on updated information in a revised VRC01 Investigator's Brochure. These changes are included in this version of the protocol.

A Study product description and storage temperature updated in Section 6.2, *Study product formulation*

The study product description in Section 6.2, *Study product formulation*, 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 addition, VRC01 storage temperatures have been updated per the revised Investigator's Brochure.

B Holding times for study products after preparation updated in Sections 6.3 and 6.4

Time limits on storage of prepared IV bags have been updated in Sections 6.3.1, 6.3.2, and 6.3.3 (concerning study product preparation) and in Section 6.4 (concerning study product administration).

C Minimum infusion time updated in Section 6.4, *Administration*

Instructions regarding equilibration of study product to room temperature have been clarified as has specification of allowable room temperature. The typical infusion time range has been revised to 15 to 60 minutes.

D In-line filer set requirement added in Section 6.4

Requirement to use an in-line filter infusion set has been added (with a cross-reference to Study Specific Procedures for information on filter specifications and additional details).

E Non-use of vials with visible particles clarified in Sections 6.3.1 and 6.3.2

Two study product preparation sections have been updated to clarify that VRC01 vials containing "visible" particles are not to be used.

Item 28 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 703/HPTN 081 are described below.

Date: August 25, 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 Revised in Section 2.4.5, *Trial monitoring*: Feasibility assessment

Item 4 Updated in Sections 2.9, 2.9.3, 2.9.4, 2.10, and Appendix A: VRC01 clinical experience in HVTN 104

Item 5 Updated in Section 2.9.5, *Particle formation*, and Section 6.2, *Study product formulation*: Product description and formulation/preparation instructions

Item 6 Revised in Section 4.7.3: *Monitoring for futility to assess PE*

Item 7 Clarified in Section 5: Eligibility determination

Item 8 Clarified in Section 5.2, *Exclusion criteria*: Tissue or organ transplantation exclusion criterion

Item 9 Clarified in Section 6.4, *Administration*: IV bag label weight and IV tubing flushing

Item 10 Clarified in Section 7.3, *Enrollment and infusion visits*: Timing of HIV infection assessment and HIV testing

Item 11 Updated in Section 7.10, *Assessments of reactogenicity*, Section 10.2.2, *AE reporting*, and Section 15, *Document references (other than literature citations)*: DAIDS AE grading table version and exceptions

Item 12 Updated in Sections 10.2: URLs for referenced documents

Item 13 Updated in Section 10.2.3: *Expedited reporting of adverse events to DAIDS*

Item 14 Updated in Section 14: *Version history*

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

Item 16 Updated in Section 16: *Acronyms and abbreviations*

Item 17 Updated in Appendix A, *Sample informed consent form*: Minimum infusion time

Item 18 Corrected in Appendix A, *Sample informed consent form*: Blood draw volumes

Item 19 Clarified in Appendix A, *Sample informed consent form*: Early termination

Item 20 Revised in Appendix B, *Approved birth control methods (for sample informed consent form)*: Approved contraception methods

Item 21 Corrected in Appendix D, *Tables of procedures (for sample informed consent form)*: Procedure timepoint

Item 22 Clarified in Appendix F: DBS allowance applies to Visit and 56-day blood draw totals

Item 23 Updated in Appendices F through I: Assay locations and HVTN laboratory listings

Item 24 Revised in Appendices G, H, K, and L: Table format and Schedule 3 blood draws at Visit #.X

Item 25 Clarified in Appendices J and M: Provision of HIV test results

Item 26 Added as Appendix N: Protocol signature page

Item 27 Updated in Sections 6.2 through 6.4 per Clarification Memo 1 to protocol Version 2.0: Study product description, storage, and administration instructions

Item 28 Corrected: Minor typographical, grammatical, and formatting errors

Date: March 8, 2017

Protocol version: Version 2.0
Protocol modification: Clarification Memo 1

Item 1 Updated in Section 6.2, *Study product formulation*: VRC01 description and storage temperature

Item 2 Revised in Sections 6.3 and 6.4: Holding times for study products after preparation

Item 3 Updated in Section 6.4, *Administration*: Minimum infusion time period

Item 4 Added in Section 6.4, *Administration*: In-line filter set requirement

Item 5 Clarified in Sections 6.3.1 and 6.3.2: VRC01 vials with visible particles not to be used

Date: June 24, 2016

Protocol version: Version 2.0
Protocol modification: Full Protocol Amendment 1

Item 1 Study population limited to women in sub-Saharan Africa at risk of acquiring HIV through sexual transmission

Item 2 Added in Section 1, *Overview*: Note regarding enrollment numbers

Item 3 Revised in Section 1, *Overview*, and Section 5.1, *Inclusion criteria*: Participant age range

Item 4 Updated in Section 1.1, *Protocol Team*: Membership and affiliations

Item 5 Clarified in Section 2.1, *Rationale for trial concept*: Worldwide HIV infections and licensure status of VRC01

Item 6 Updated: Section 2.4.5, *Trial monitoring*

Item 7 Updated: Section 2.6, *Plans for future product development and testing*

Item 8 Added in Section 2.8.1, *Protection against* challenge *in NHP models*: Non-neutralizing mechanisms of bnAb protection in NHP challenge studies

Item 9 Added in Section 2.9.2, *VRC 602*: Information on serum neutralizing activity and anti-VRC01 antibodies

Item 10 Updated in Sections 2.9.3 and 2.9.4: Phase 1 clinical trial experience and VRC01 safety summary

Item 11 Added in Section 2.9.3: VRC01 pharmacokinetics in HVTN 104

Item 12 Revised in Sections 3.3, 4.8, and 9.6 and Appendix F: PrEP use monitoring

Item 13 Revised: Section 4, *Statistical considerations*

Item 14 Clarified in Section 5.1, *Inclusion criteria*: Urine protein measures

Item 15 Revisions in Section 5.2: *Exclusion criteria*

Item 16 Clarified in Section 5.3.3, *Discontinuing infusions for a participant*: Participants for whom infusions are stopped for reasons other than HIV infection

Item 17 Updated in Section 6, *Study product preparation and administration*: Study product regimen, formulation, storage, preparation, and administration instructions

Item 18 Removed in Section 7.2, *Pre-enrollment procedures*: Required recording of generic names for concomitant medications

Item 19 Clarified in Section 7.3, *Enrollment and infusion visits*: Urine dipstick and instructions for infusion observation and reactogenicity assessment

Item 20 Corrected in Section 7.4: *Post-infusion visits* for *HIV-uninfected study participants*

Item 21 Corrected in Section 7.5, *HIV counseling and testing*: PrEP information source

Item 22 Clarified in Section 7.5.1, *Study product-related seroreactivity*: Serum concentrations tested and reference to HIV testing only

Item 23 Added as (new) Section 7.6: Follow-up visits for HIV-infected participants

Item 24 Added as (new) Section 7.7 and Appendices I and M: *Follow-up for study participants for whom infusions have been stopped for reasons other than HIV infection*

Item 25 Corrected in Section 7.8, *Contraception status*: Where to find details regarding contraception requirements

Item 26 Clarified in Section 7.9 and Appendices F, I, J, and M: Urine testing

Item 27 Clarified in Sections 7.10, *Assessments of reactogenicity*: Systemic and local signs and symptoms and infusion sites reactions

Item 28 Revised in Section 7.11, *Visit windows and* missed *visits*: Visits for performance of safety assessments and local safety labs

Item 29 Corrected in Section 8.5, *HIV infection during* the *study*: Visit schedules for HIV-infected study participants

Item 30 Revised in Section 9.5.1, *Anti-VRC01 antibody* assay: Assay description

Item 31 Clarified in Section 9.5.2, *Neutralizing antibody* assay: Range of applicability

Item 32 Clarified in Section 10.1.1, *HVTN 703/HPTN* 081 *PSRT*: Protocol safety review team membership

Item 33 Removed in Section 10.1.3, *Roles and responsibilities in safety monitoring*: Reference to planned holds

Item 34 Added in Section 10.2.2, *AE reporting*: Uterine bleeding secondary to contraception

Item 35 Added in Section 10.2.2, *AE reporting*: African working hours

Item 36 Updated in Section 10.2.3, Expedited reporting of adverse events to DAIDS: DAERS support email address

Item 37 Corrected in Section 10.4.2: PSRT review timing

Item 38 Clarified in Section 10.4.3: Cumulative safety data reports to DSMB

Item 39 Removed in Section 10.6, *Social impact reporting*: Reference to Study Specific Procedures (SSP)

Item 40 Updated in Section 15: URL for DAIDS source documentation requirements

Item 41 Updated and clarified: Appendix A, Sample informed consent form

Item 42 Added in Appendix A and (optional) Appendix E: Consent for HIV-infected study participants

Item 43 Clarified in Appendix A and C consent forms: Potential genetic testing

Item 44 Added in Appendix A, C, and E consent forms: MCC contact information

Item 45 Added in Appendix B, *Approved birth control methods*: Injectable contraceptives

Item 46 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 47 Clarified in footnotes to Appendix F and J: Pregnancy testing

Item 48 Clarified in Appendices F, G, and I: HVTN and non-HVTN endpoint laboratories

Item 49 Added in Appendix F: VRC lab for anti-VRC01 antibody levels

Item 50 Corrected in Appendices G, H, K, and L: Appendix titles, visit schedules, visit numbering, and procedures

Item 51 Added in Appendices G and H: Whole blood samples for confirmatory HIV testing

Item 52 Clarified in Appendix J, *Schedule 1*—Procedures *at CRS for HIV-uninfected participants*: No participant questionnaire at Visit 0 (screening visit)

Item 53 Added to Appendices K and L: Local lab assessments

Item 54 Updated and corrected throughout the protocol document: Acronyms, abbreviations, numbering of figures, tables, and appendices, cross-references, and grammatical errors

Date: April 15, 2016

Protocol version: Version 1.0
Protocol modification: Clarification Memo 2

Item 1 Clarified in Appendix I, *Schedule 1—Procedures at CRS for HIV-uninfected participants*: No participant questionnaire during screening

Date: February 22, 2016

Protocol version: Version 1.0
Protocol modification: Clarification Memo 1

Item 1 Corrected in Appendices G, H, J, and K: Visit numbering

[*Note: Clarification Memo 1 dated February 22, 2016 replaces Clarification Memo 1 dated September 4, 2015 and Letter of Amendment 1 dated September 28, 2015.*]

Date: September 28, 2015

Protocol version: Version 1.0
Protocol modification: Letter of Amendment 1

Item 1 Corrected in Appendices G, H, J, and K: Visit schedules

Item 2 Clarified in Appendices J and K: Assessment of HIV/AIDS-related conditions applies to both complete and abbreviated physical exams

Item 3 Removed in Appendices J and K: Social impact assessment questionnaire

Date: September 4, 2015

Protocol version: Version 1.0
Protocol modification: Clarification Memo 1

Item 1 Corrected in Appendices G, H, J, and K: Visit numbering

Item 2 Corrected: Titles of Appendices J and K

Date: August 11, 2015

Protocol version: 1.0
Protocol modification: NA