June 24, 2016

Full Protocol Amendment 1

A summary of changes to

Protocol

Version 2.0

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.

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.

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

Reviews of HVTN 703/HPTN 081 by national regulatory agencies revealed regional differences in perspective on the protocol. In order to address these differences, the study has been divided into two regionally separate but otherwise comparable protocol versions: (1) a revised HVTN 703/HPTN 081 protocol for sub-Saharan African women; and (2) a separate protocol (HVTN 704/HPTN 085) for men and transgender persons in the Americas and Switzerland who have sex with men. While the protocols are now separate, the original plan to evaluate efficacy in the two cohorts separately and then together remains in place. For this reason, the two protocols are being kept as closely aligned with each other as possible. Dividing the study into two protocols is intended to allow regulatory authorities in each region to focus their reviews and guidance on issues particularly applicable to the populations for which they are responsible. Division of the study into two separate protocols has necessitated the following revisions to HVTN 703/HPTN 081.

A Protocol title revised on title page, in Section 1, *Overview*, and in Appendix A, C, and E sample consent forms

B Primary objectives revised in Section 1, *Overview*, and in Section 3.1, *Primary objectives and endpoints*

Primary objectives 1 and 2 have been revised to specify the study population and to remove mention of "the two cohorts."

C Schema revised in Section 1

Table 1-1, *Schema*, has been revised by:

- Removing the "Cohort" column;
- Removing rows for the MSM & TG cohort (ie, formerly Groups 1, 2, and 3);
- Renumbering the remaining rows (formerly Groups 4, 5, and 6) Group 1, Group 2, and Group 3;

- Revising the total sample sizes for each VRC01 dose group, for controls, and for the trial as a whole, and

- Removing definitions of MSM and TG from immediately below the schema.

D "Participants" revised in Section 1, *Overview*

Descriptions of the study population composition and sample size have been revised.

E Mention of "two cohorts" and of MSM+TG removed throughout Section 2, *Background*

Mention of two cohorts and of MSM+TG has been removed throughout the background section of the protocol.

F *Cohort selection* revised in Section 2.4.1

Discussion of "cohorts" has been removed from the first paragraph, description of HIV incidence in MSM+TG in the second paragraph has been removed, and description of HIV incidence and disease burden among sub-Saharan African women has been expanded. Notation that a parallel study is being conducted among MSM+TG has been added at the end of this section.

G *Trial monitoring* revised in Section 2.4.5

In light of the revised sample size, the threshold for the early feasibility check has been changed from approximately 240 participants to approximately 120 participants and references to individual cohorts and pooling across cohorts has been removed.

H Section 2.5, *Combination prevention for HIV acquisition* revised

Section 2.5 has been revised to highlight the HIV incidence and disease burden among women in sub-Saharan Africa and to clarify the contents of the HIV prevention package that will be offered to all study participants. Section 2.5.1 has been retitled *Evidence for PrEP efficacy* and has been revised to summarize the clinical trial evidence for PrEP efficacy, especially in women, including a figure describing a recent meta-analysis. A new Section 2.5.2, *Evolving PrEP guidelines,* has been added, along with a new Section 2.5.3, *Operationalizing PrEP access in sub-Saharan Africa,* which describes current policies regarding PrEP in sub-Saharan African countries and the protocol team's determination to work collaboratively with national regulatory and other authorities to develop appropriate mechanisms by which trial participants can be given access to PrEP.

I Reference to separate cohorts removed from Section 2.8.1, *Protection against challenge in NHP models*

J Reference to "Cohorts" and "MSM+TG" removed throughout Section 4, *Statistical considerations*

References to multiple trial cohorts and references to MSM+TG have been removed throughout Section 4. These revisions include (noting that many of the sections, tables, and figures have been renumbered from Version 1 of the protocol):

- Deletion of the second paragraph in Section 4.1, *Outline of the statistical considerations section*.
- Deletion of mention of "cohorts" in Section 4.2, *PE parameters for measuring mAb efficacy and associated primary and secondary hypothesis tests,* and of hypothesis tests for both cohorts pooled together in the last paragraph of this section.
- Deletion in Section 4.4, *Sample size calculations for testing for overall PE (Primary objective 2),* of text describing trial power to test for overall efficacy in each cohort separately and pooled across cohorts.
- Deletion in Section 4.4.1, *Assumptions of the sample size calculations including sequential monitoring for PE,* of discussion of cohorts and also of incidence assumptions for the MSM+TG cohort.
- Deletion of cohort specification in the text of Section 4.4.2, *Power curves and operating characteristics of the design (Primary objective 2),* including in the captions to Figure 4-1 and Table 4-1.
- Removal from Table 4-1 in Section 4.4.2 of the row containing cohort definitions and the column describing study power in the MSM+TG cohort. The table has also been extended to include 90% and 95% effect sizes and the remaining estimates of study power have been updated per revised assumptions about the pace and duration of trial enrollment.
- Removal of (former) Figures 4-2, 4-4, 4-6, and 4-8 describing the operating characteristics of the trial design in the MSM+TG cohort along with the text referring to those figures in Sections 4.4.2, 4.4.3, 4.4.4, and 4.4.5.
- Updating in Sections 4.4.2 through 4.4.5 of (renumbered) Figures 4-1 through 4-4 with references to "cohort" removed from the figures and captions. Note that these figures showing trial operating characteristics have also been updated per revised assumptions about the pace and duration of trial enrollment
- Removal in Section 4.4.4, *Additional operating characteristics of the primary analysis accounting for sequential monitoring,* of (former) Table 4-2 describing the probabilities of different trial outcomes among the MSM+TG cohort.

- Removal of cohort specification from the caption to (renumbered) Table 4-2 in Section 4.4.4, extension of the table to include effect sizes of 90% and 95%, and recalculation of probabilities of reaching each trial outcome recalculated.

- Removal from (renumbered) Table 4-3 in Section 4.4.4 of rows describing the number of infection endpoints expected among MSM+TG, removal of mention of cohorts from the caption, and expansion of the table to include endpoint infections during the entire 210 week trial duration (80 weeks per participant for purposes of PE and 130 weeks projected accrual).

- Deletion from Section 4.4.6, *Rationale for HIV-1 incidence assumptions*, of discussion of assumptions about incidence among MSM+TG. Added text describes the impact on study power of lower than predicted HIV incidence (potentially associated with increasing PrEP uptake). Description of the currently uncertain prospects for wide-scale PrEP rollout in this region has also been added to this section.

- Removal of the cohort column from (renumbered) Table 4-4 in Section 4.5, *Power for the secondary analysis comparing HIV-1 incidence between the 10 mg/kg mAb group versus the 30 mg/kg mAb group,* along with rows for MSM+TG and cohorts combined. Discussion of cohorts has also been removed from the text of this section.

- Removal in Section 4.6, *Sample size calculations for safety*, of all mention of cohorts in the section text and in the caption of (renumbered) Table 4-5. Renumbered Table 4-5 shows power to detect SAEs for the revised study population only.

- Removal of references to cohorts in Section 4.7, *Monitoring of the trial* and in the first paragraph of Section 4.7.1, *Role of the Data Safety Monitoring Board (DSMB)*.

- Removal of reference to study cohorts from the caption to (renumbered) Figure 4-6 in Section 4.7.1.1.

- Revision in Section 4.7.2, *Feasibility check and guideline for continuing enrollment as planned*, of the trigger for "feasibility monitoring" from the first 240 to the first 120 enrolled participants reaching Week 32 (see Item 1G above).

- Deletion of cohorts from Section 4.7.3, *Monitoring for failure to assess PE*, including from the enrollment rate, dropout rate, and infection rate parameters for calculating Time to Target Number of Infections (TTNI).

- Deletion of "cohort" from Section 4.8, *Assessment of PrEP use.*

- Removal of analyses of efficacy and mention of cohorts in Section 4.11.6, *Specific approach to assessing PE, PE10, PE30* and Section 4.11.7, *Assessment of individual-level markers of VRC01 mAb that correlate with protection against HIV infections (Secondary objective 1).*

- Deletion of cohorts from Section 4.11.7.4, *mAb markers*.

- Deletion of cohorts from captions of Figures 4-8 and 4-9 and from the text in (retitled) Section 4.11.7.5, *Statistical power for assessing a mAb marker as a correlate of protection*. Figures and captions have also been revised to reflect the revised sample size and anticipated numbers of cases and controls for correlates assessments.

- Deletion of pooling over cohorts from Section 4.11.7.6, *Genotypic and phenotypic sieve analysis*.

- Deletion of pooling over cohorts from Section 4.11.7.7, *Illustration of power to detect a phenotypic sieve effect*.

K Inclusion criteria 9 and 10 revised in Section 5.1, *Inclusion criteria*

Specifications of region and text pertaining to the MSM+TG cohort have been removed from Inclusion criteria 9 and 10.

L "Cohorts" removed from Section 6, *Study product preparation and administration*

Text pertaining to "cohorts" has been removed from Section 6.1, 6.3.1, 6.3.2, and 6.3.3. Per revisions to the Schema (see Item 1C), Groups 4 through 6 have been removed from Section 6.1 and in the headers to Sections 6.3.1, 6.3.2, and 6.3.3. Thus, treatment assignments T4, T5, and C6 in Version 1.0 of the protocol become T1, T2, and C3 in Version 2.0. This change is shown in notes in the headers to Groups 1 through 3 in Section 6.1.

M Group/Treatment assignment changes documented in Section 6.1: *Study product regimen*

Notes have been added to Section 6.1 indicating the reassignment of study participants randomized to Groups 4-6 under protocol Version 1.0 to Groups 1-3 in Version 2.0. The notes also indicate that treatments for these participants do not change. In addition, instruction has been added to the end of this section regarding documentation of group reassignment for these participants.

N Reference to "born female" removed from Section 7.2

Since all persons enrolled in this trial will be female, specification of pregnancy prevention for participants "born female" is redundant has been removed.

O STI testing for MSM+TG removed in Section 7.3, *Enrollment and infusion visits*, in Section 12 of Appendix A, *Sample informed consent form*, and in the tables and footnotes in Appendices F and J

Description of STI testing in Section 7.3 along with the STI testing schedule and accompanying footnotes 11-14 in Appendices F and J have been revised for appropriateness to the revised study population.

P Reference to North and South America removed from Section 13

Q Reference to "women" removed from Section 13.1

As all study participants will be women, specifying "women" in this section is redundant and has been removed.

R Certificate of confidentiality removed from Section 13.6, *Protect private/confidentiality*

Text describing the US-specific Certificate of Confidentiality has been removed from Section 13.6.

S Appendix A, *Sample informed consent form*, revised

In addition to the revised protocol title, changes in Appendix A prompted by restriction of the study population to women in sub-Saharan Africa include:

- Addition of a notice that a similar study will be conducted among MSM and transgender people in North America, South America, and Switzerland and revision of the total sample size under "About the study";
- Revision of description of groups under Section 10;
- Removal of text specific to US sites from Sections 9 and 15,
- Removal of Groups 4 through 6 from the "Infusion schedule" table in Section 11;
- Revised description of STI testing in Section 12;
- Removal of text specific to Americas/Switzerland sites from Section 14;
- Addition of information about PrEP in sub-Saharan Africa in Section 15, including notation of FTC/TDF licensure in South Africa and Kenya, indication that it is effective if taken every day, and of its availability in the private sector and through demonstration projects in South Africa–a site prompt has been added advising sites outside South Africa sites to revise this section to fit local conditions;
- Removal in Section 20 of the US FDA from the list of groups that can access study records, of US-specific test regarding certificates of confidentiality, and of test regarding FDA-required clinical trial registration; ;
- Removal from "Risks of genetic testing" in Section 22 of information specific to US research sites; and
- Removal from Section 27 of text regarding study-related injuries specific to sites outside Africa.

T Title revised in Appendix B, *Approved birth control methods (for sample informed consent form)*

Since only African women will be enrolled in the revised study, specification of "for African women" has been removed from the title to Appendix B.

U Removed: Appendix C, *Approved birth control for transgender men (for sample informed consent form)*

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

Because of the randomization scheme used this trial, we cannot ensure that exactly the same number of study product and control recipients will be enrolled. A note to this effect has been added immediately below Table 1-1, *Schema*. In addition, unique markers have been assigned to the three footnotes to Table 1-1.

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

Because younger women in southern Africa are generally at higher risk of HIV infection and in order to enhance statistical power to assess the efficacy of VRC01 in preventing HIV infection, the upper age limit for participation in this trial has been reduced from 50 to 40 years of age.

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

Protocol Team membership has been updated in Section 1.1. In addition, some institutional affiliations have been corrected and formatting has been made more consistent.

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

At the suggestion of the study sponsor, a WHO estimate of new HIV infections worldwide (2014) has been added to the first paragraph, clarification that the burden of ARV provision is heaviest in countries bearing the highest burden of HIV disease has been added, and clarification that VRC01 is not on a path to licensure has been added as a new paragraph at the end of this section. Also at the suggestion of the study sponsor, discussion of long acting injectable ARVs in HIV prevention trials has been removed from the second paragraph. A statement that participants should expect no direct benefit from the study drug has been deemed unnecessary and has been removed. This statement has also been removed from Section 2.4.

Item 6 Updated: Section 2.4.5, *Trial monitoring*

Revisions in this section include:

- "Operational futility" has been replaced with "futility for assessing prevention efficacy";

- Clarification that monitoring for potential harm involves comparison of HIV infection rates between VRC01 recipients and the control group;

- Monitoring for harm is specified as beginning with the 20th total infection in the pooled study groups (see Item 13F below); and

- The schedule for non-efficacy monitoring has been synchronized with the expected DSMB meeting schedule (see Item 13G below).

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

Minor changes have been made in the second paragraph of this section, including:

- Notation that the cited factors could also influence advanced development of antibodies similar to VRC01;

- Notation that derivatives of VRC01 might potentially be used in combination with other neutralizing mAbs; and

- Addition that the further development is likely to include improving potency as well breadth of neutralization.

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

In support of the hypothesis that the 10 mg/kg IV infusion dose of VRC01 may provide protection against HIV-1 infection, we have added to the end of Section 2.8.1 a summary discussion of evidence from NHP challenge studies that cellular effector functions mediated by bnAbs such as VRC01 may provide greater protection from infection than would be predicted by in vitro neutralization assays alone.

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

Notation has been added at the end of this section that in study VRC 602, VRC01 retained the expected HIV neutralizing activity in serum and that no anti-VRC01 antibodies were detected.

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

The number of participants enrolled has been updated and more details have been provided regarding the safety record of VRC01 in HVTN 104. The safety summary in Section 2.9.4 has been updated similarly. Finally, a statement that most infusion-related events occur within the first 24 hours after administration has been removed from Section 2.10.

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

New Figure 2-9 showing VRC01 pharmacokinetics (PK) to 4 months after the first 10mg/kg and 30mg/kg infusions in HVTN 104 has been inserted along with text summarizing PK findings to date in that study. Finally, cross-references to Section 2.9.3 and Figure 2-9 have been added to Section 2.4.2, *Dose and schedule*.

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

A Revisions to Section 3.3, *Exploratory objectives*

Exploratory objectives 1 and 2 have been revised to reflect the fact that the dried blood spot method being instituted for PrEP monitoring tests specifically for tenofovir use and does not test for consumption of other antiretroviral (ARV) drugs.

B Revisions to Section 4.8, *Assessment of PrEP use*

Text describing possible methods of ARV monitoring has been replaced with description of dried blood spot sampling for PrEP monitoring using a calendar-based selection of visits to ensure sampling of participants across the visit schedule at all sites throughout the study. This section also now includes reference to the study monitoring plan, a non-protocol document. Clarification that reports of PrEP use will be provided to the DSMB and the Oversight Committee and that the protocol team leadership will see treatment-pooled PrEP drug use summaries has been added as well.

C Revised in Section 9.6, *ARV detection*: Assay and sampling plan description

This section has been revised to reflect replacement of the previously described high throughput HRMS analysis with assessment of intracellular levels of tenofovir diphosphate, a TFV metabolite, in red blood cells recovered from dried blood spots. Because this assay provides more information about regularity of FTC/TFV use over a longer period of time, it supports more precise evaluation of PrEP use in the study population and potential impacts on HIV incidence and endpoint accrual.

D Revisions in Appendix F, *Schedule 1—Laboratory procedures for HIV-uninfected participants*

The table of laboratory procedures in Appendix F has been revised to reflect adoption of collection of dried blood spots from a random sample of study participants at regular timepoints. These changes include: addition of a row labeled “ARV detection by dried blood spots” with a 2mL EDTA tube specified, CSR specified as the “ship to” and UCT and UC Denver under “assay location”, and visits 2-26 grayed out with “See footnote 16” added; revision of “ARV detection” to “ARV detection by serum or plasma”; addition of University of Cape Town and University of Colorado, Denver to the list of non-HVTN endpoint labs in footnote 2 (and to the list of endpoint laboratories in Section 1); adding an explanatory footnote 16; adding footnote 17 explaining how blood collection for dried blood spots is accounted for in the 56-day blood draw totals.

Item 13 Revised: Section 4, *Statistical considerations*

In addition to revisions in Section 4 attendant on redefinition of the study population (see Item 1K above), revisions and clarifications have been made to the statistical tests specified for primary and secondary efficacy analyses, sample size calculations, randomization stratification, monitoring, and analysis plans. These changes are summarized below. Note that, because of the redefined study population and removal of several figures and tables, the remaining figures and tables have been renumbered.

A Primary analyses of PE changed from 1-sided to 2-sided tests

The protocol statisticians have determined that 2-sided testing is more appropriate for primary efficacy analyses because if negative PE is detected for either dosing level, there would be interest in reporting this result. Hence, the primary and secondary tests have been changed from 1-sided tests of a null hypothesis ($PE \leq 0$) versus the alternative hypothesis ($PE > 0$) using 1-sided alpha = 0.025 to a 2-sided test of a null hypothesis ($PE = 0$) versus the alternative ($PE \neq 0$) using 2-sided alpha = 0.05. This change has been made in Section 4.2, *PE parameters for measuring mAb efficacy and associated primary and secondary hypothesis tests*, in description of supportive analyses using targeted maximum likelihood estimates (tMLE) in Section 4.11.4.1, *General approach*, and in Section 4.11.6, *Specific approach for assessing PE, PE10, PE30*.

B 2-sided tests specified for calculations of sample size for sequential PE monitoring and safety analyses

Specification of 2-sided tests has been added to sample size calculations for sequential monitoring in Section 4.4.1, *Assumptions of the sample size calculations including sequential monitoring for PE*, and for sample size calculations for safety analyses in Section 4.6, *Sample size calculations for safety*. Notation that the cumulative hazard-based Wald tests for comparing HIV incidence between the dose groups is "2-sided" has been added to the second footnote to Table 4-4 in Section 4.5.

C 1-sided tests specified as basis for power calculations for primary and secondary efficacy objectives

The statisticians have determined that power calculations should be based on 1-sided tests as the primary interest is in power to detect positive values of PE. This specification has been added in Section 4.4, *Sample size calculations for testing for overall PE (Primary objective 2)*, and throughout Section 4.4.1 – 4.4.5 which describe the operating characteristics of the study design. This includes the captions of Figures 4-1 through 4-4 and Tables 4-1 and 4-2.

D Multiplicity adjustment added in Sections 4.2 and 4.11.6

In addition to unadjusted p-values, Holm-Bonferroni p-values will be reported for each of the individual dose versus placebo group analyses. This change was made at the suggestion of the US FDA.

E Comparison between power of 2- and 3-arm designs added in Section 4.3 and 4.4.2

Notation that power to reject the null hypothesis is similar in 2- and 3-arm designs with the same number of study drug and placebo recipients has been added to the first paragraph in Section 4.3. A more detailed explanation of why this is so and why differential efficacy between the dose groups provides slightly greater power and efficiency has been added to the end of Section 4.4.2.

F Sequential monitoring revised in Sections 4.4.1 and 4.7.1.1

In Section 4.4.1, *Assumptions of the sample size calculations including sequential monitoring for PE*, and in Section 4.7.1.1, *Sequential monitoring of PE for potential harm, non-efficacy, and high efficacy*, the description of potential harm monitoring has been modified to pool over the two mAb dose groups in order to harmonize with the plan for the other types of sequential monitoring for prevention efficacy. In addition, the testing approaches, stopping boundaries, and timing of interim analyses have been clarified in Section 4.7.1.1 and in Table 4-6, *Summary of sequential monitoring of PE*. Clarification of stopping boundaries has been added to the caption to Figure 4-6. The rationale for the approach taken has been expanded in this section as well. Note also that, for clarity, "efficacy futility" has been replaced by "non-efficacy" throughout the sections concerning sequential monitoring. Reference to the planned HVTN 701 trial has been removed.

G Frequency of DSMB meetings and content of reports to DSMB updated in Sections 4.7.1 and 4.7.3

The Data and Safety Monitoring Board (DSMB has regular 6-monthly meeting and has agreed to that schedule for this study. This change is indicated in Section 4.7.1, *Role of the Data Safety Monitoring Board (DSMB)*, Section 4.7.3, *Monitoring for futility to assess PE*, and in Table 4-6. In addition, a description of reports to the DSMB has been added to Section 4.7.1. This includes addition of an "early safety check" should 20 participants reach their Week 12 visit prior to the first scheduled DSMB meeting and a formal interim safety assessment of a "safety run-in cohort." Specification in the first paragraph of Section 4.7.1 that the DSMB will review "unblinded" data has been removed since whether full unblinding is at the express discretion of the DSMB.

H Monitoring for futility to assess PE revised in Section 4.7.3

For greater clarity, "operational futility" has been replaced by "futility to assess PE" throughout this section, including the title. The metric for this monitoring has been revised from 90% power to 70% power to reject the null hypothesis PE $\leq$ 0% if PE = 60% in the primary analysis. The number of endpoint infections required for such power has been revised from 60 to 29. In addition, description at the end of this section of the feasibility check has been revised for clarity and appropriateness to the revised study population.

I Randomization stratification revised in Section 4.9, *Randomization*

Given the large number of study sites and the expectation that few (or no) HIV-1 infection endpoints may occur at some study sites, statement that randomization will be stratified by study site has been removed from this section.

J Approach to primary and secondary analyses revised in Section 4.11.4.1

Section 4.11.4.1 has been modified to specify hazard-ratio based secondary prevention efficacy analyses with score tests stratified by VRC01 dose group using as failure time the time from most recent infusion to estimated date of HIV infection as a time-dependent covariate in a Cox proportional hazards model. This model will also be used for a secondary analysis of prevention efficacy in subgroups defined by cumulative infusion adherence over time included as a time-varying covariate. In addition, use of a log-rank test and a Gehan-Wilcoxon test stratified by dose group to test the sensitivity analysis has been added in the final paragraph in this section.

K Reference to antigen reagents added in Section 4.11.7

Notation that effector function markers may inform selection of antigen reagents for future HIV vaccine trials has been added in the final paragraph in this section.

L mAb marker sampling revised in Section 4.11.7.1, *Sampling of mAb markers*

Text describing the sampling plan for mAb or immune responses to mAb has been rewritten so that the sampling design can be revised depending on outcomes of the primary efficacy analysis, thus affording an opportunity to increase the statistical efficiency of the analysis and to account for scientific priorities in the sampling design. For these reasons, specification of the percentage of participants from each group to be samples and the timepoints of sampling has been removed.

M Revised in Section 4.11.7.2, *Overview of the analysis of a mAb marker as a correlate of protection*

Description of this section as a brief summary has been added along with a statement that the full plan will be finalized without using any information on the case-control status of participants. In addition, a statement has been added at the end of the section that the analysis will account for how adherence to the infusion schedule affects the modeling of marker characteristics over time postenrollment.

N Added in Section 4.11.7.3, *A time-window approach to assessing mAb correlates of protection*

Description of how mAb correlates of protection will be assessed has been substantially expanded in Section 4.11.7.3. Additions include more detailed description of the strengths and weaknesses of different time-window approaches to correlates analyses.

O Text and Figure 4-7 revised in Section 4.11.7.4, *mAb markers*

Figure 4-7 has been revised to show a logo plot of the VRC01 antibody footprints that occur in 444 subtype C HIV-1 sequences from sub-Saharan Africa in the Los Alamos National Laboratory HIV sequence database rather than the partial logo footprints for clade B sequences shown previously. Description of this figure in the text has been revised accordingly.

P Revised in Section 4.11.7.5, *Statistical power for assessing a mAb marker as a correlate of protection*

Assumptions about the number of cases and controls for correlates assessments have been revised. Power curves in Figures 4-8 and 4-9 have been recalculated based on revised effect sizes. These assumptions have been clarified in the figure captions. The captions have also been revised to include the PE levels considered and to indicate the size of the study population from which the specified numbers of cases and controls will be drawn. Notation has also been added in text that the assay noise parameter 'rho' includes noise due to uncertainty regarding the exact time of HIV infection. In addition, the second paragraph in this section has been revised to clarify that data from diagnostic testing kits is incorporated into modeling of monoclonal antibody markers and HIV infection times and into the statistical analysis of prevention efficacy associated with such markers.

Q Additional sieve analyses added to Section 4.11.7.6, *Genotypic and phenotypic sieve analysis*

Following Figure 4-10, descriptions of two additional types of sieve analysis have been inserted. The first type focuses on effector functions and the second assesses PE against HIV-1 strains that are sensitive to VRC01 neutralization and differential PE for HIV-1 strains that are sensitive versus resistant to neutralization and to other non-neutralization effector functions (eg, ADCC, ADCP). In addition, the panels in Figure 4-10 have been recalculated and clarification that genotypic sieve analysis is defined by mismatches to the subtype C consensus sequence has been added.

R Revised in Section 4.11.7.7, *Illustration of power to detect a phenotypic sieve effect*

The "Moderate" to "Maximal" terminology used to describe effect sizes in the text and in Figure 4-11 has been replaced by Effect Sizes "1" through "4". Arguments for the biological plausibility of Effect Size 3 have been added following Figure 4-11. In addition, Table 4-7 has been inserted, showing the percentages of fully susceptible and fully resistant HIV-1 strains at each of the four Effect Sizes being modeled. Notation has been added that sieve analyses will include all MITT infected participants as well as mAb-group infected participants who received an infusion at the beginning of the 8-week period during with their infection was diagnosed.

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

To account for urine dipstick kits that provide semi-quantitative readouts, the allowable "semi-quantitative" urine protein measure has been added to Inclusion criterion 14 in Section 5.1

Item 15 Revisions in Section 5.2: *Exclusion criteria*

A Added: PSRT may permit exceptions to Exclusion criterion #4

As there are certain circumstances under which a volunteer who has indeterminate HIV screening test results may nevertheless be appropriate for trial enrollment, PSRT approval of exceptions to this exclusion criteria has been added.

B Removed: Previous receipt of monoclonal antibodies

Previous receipt of antibodies has been removed as an exclusion criterion as this is not a contraindication to administration of licensed monoclonal antibodies and prior receipt appears to pose no threat of confounding the trial results. Accordingly, the header for this section of Exclusion criteria has been revised to "Vaccines."

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

To avoid potential confusion, cross references to Schedule 2 and Schedule 3 laboratory and clinic procedures schedules have been removed. In addition, mention of Schedule 4 for participants for whom infusions are discontinued for reasons other than HIV infection has been added to this section.

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

Based on ongoing stability studies and information in the updated Investigator's Brochure, instructions regarding VRC01 thawing, particle formation, preparation, stability, storage, and administration have been updated in Sections 6.2, 6.3.1, 6.3.2, 6.3.3, and 6.4. In addition, the treatment descriptions in Section 6.1 have been revised to clarify that the specified volume is a preparation target rather than a restriction on volume administered. Similarly, the final paragraph in Section 6.4 has been revised to clarify that the entire volume of study product prepared in the pharmacy should be administered in the clinic.

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

Because the HVTN is moving to a coding system for concomitant medications in which trade names and generic names will be allowed, language requiring recording of the complete generic name for all concomitant medications has been removed from the third bullet in this section.

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

A cross-reference to Section 7.9, *Urine testing*, has been added to the final bullet in Section 7.3 and the third and fourth paragraphs following the first set of bullets in Section 7.3, concerning reactogenicity assessments, have been edited for clarity.

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

The procedures listed in Section 7.4 apply only to study participants who remain HIV-uninfected. Accordingly, the section title and the first sentence in the section have been

revised. In addition, cross-references to laboratory and clinic procedures appendices have been corrected in the sentence following the first set of bullets, and the urine dipstick procedure, which was inadvertently omitted, has been added.

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

A reference to the SSP as a source for more detailed information on PrEP provision and referrals has been removed.

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

In the first paragraph, the range of serum concentrations tested for reactivity on common HIV test kits has been updated. In the second paragraph, text has been added to clarify that the discussion concerns specifically "HIV" testing and test results.

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

As the schedule of visits and procedures for HIV-infected study participants differs significantly from that for HIV-uninfected study participants, a new Section 7.6 has been added describing Schedules 2 and 3 and cross-referencing Appendices G, H, K, and L.

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*

To eliminate a potentially excessive burden on study sites and on participants for whom infusions have been stopped permanently for reasons other than HIV infection, a new visit schedule (Schedule 4) has been added to monitor participant health and safety. This schedule entails clinic visits scheduled approximately quarterly through the remainder of the participant's 92-week study duration.

A Schedule 4 follow-up procedures described in (new) Section 7.7

A new section has been added describing procedures at scheduled study visits for participants whose infusions have been stopped for reasons other than HIV infection.

B Schedule 4 laboratory procedures added as Appendix I, *Schedule 4: Laboratory procedures for participants who discontinue infusions for reasons other than HIV infection*

C Schedule 4 clinic procedures added as Appendix M, *Schedule 4: Procedures at CRS for participants who discontinue infusions for reasons other than HIV infection*

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

Appendix B, *Approved birth control methods (for sample informed consent form)* has been identified as the source for details regarding contraception requirements.

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

The description of urine testing in (renumbered) Section 7.9 has been revised to list the analytes that should be analyzed and recorded and to clarify when urine microscopy is required. In addition, instructions have been clarified with regard to transient abnormality in dipstick results during screening, due to non-urinary bleeding (eg, menses), and due to infection.

For consistency and clarity, in Appendices F, I, J, and M, urine testing has been revised to specify "Urine dipstick" with a footnote adding "And microscopy if needed."

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

Description of reactogenicity assessment has been clarified in Section 7.10, including correcting a form name and adding a cross-reference to the SSP. In addition, text has been revised to clarify that memory aids provided to participants are neither designed nor intended to serve as source documents. In Section 7.10.1, pruritus and diarrhea have been removed from the list of systemic and local symptoms and phlebitis has been removed from the list of infusion site reactions. Note also that pruritus has been removed from the list of subjective reactogenicity symptoms in the third footnote to Table 10-1. The text in Section 7.10.2 has been revised to clarify that recording/reporting horizontal and vertical measurements applies only to redness/erythema and induration/swelling.

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

Given the structure of visit window for this protocol, a participant visit at any time will fall within a visit window. Hence, the text referring to interim (ie, out of window) visits has been removed. In its place, text has been added to the second paragraph in this section indicating that, following a missed visit, CRS staff should attempt to bring the participant in as soon as possible to complete required safety assessments and other procedures.

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

The second paragraph has been revised to clarify that infusions will be stopped permanently for participants for whom they were discontinued for other reasons but who were subsequently confirmed to be HIV-infected.

In the third paragraph in Section 8.5, the timepoints for HIV-1 RNA testing have been updated to reflect the revised Schedule 2 visit schedule.

The final paragraph in Section 8.5 has been revised to clarify the visit schedules applicable to participants who are found to have been HIV-infected at enrollment, who become HIV-2–infected following enrollment, and who are diagnosed with HIV infection while on Schedule 4 (ie, participants whose infusions have been stopped for reasons other than HIV infection).

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

The assay description in Section 9.5.1 has been revised to match the anti-VRC01 antibody assay currently in use by the VRC.

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

The text of Section 9.5.2 has been revised to clarify that application of assays to determine HIV neutralization capacity will depend on VRC01 concentrations measured in specimens and that all specimens testing positive for anti-VRC01 antibodies will be tested for HIV-1 neutralizing activity.

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

Following the bulleted list of PSRT members in Section 10.1.1, a sentence has been added clarifying that a medical officer from at least one organization designated by the study sponsor will participate in the PSRT.

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

As there are no holds planned for this study, reference to notification when "planned holds" are instituted has been removed.

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

Uterine bleeding secondary to contraception has been added to the list of AEs to be reported per the Study Specific Procedures rather than the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.

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

In the second to last paragraph, working hours during which the Core Safety Specialist (based in the USA) or Regional Medical Liaison (based in South Africa) will reply to email notification of safety events requiring immediate attention have been clarified to include South Africa Standard Time and Central Africa Time.

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

The full name of the DAERS system has been corrected in Section 10.2.3 and in Section 15 and the email address for DAERS support has been updated in Section 10.2.3.

Item 37 Corrected in Section 10.4.2: PSRT review timing

The title and text of Section 10.4.2 have been corrected to clarify that the Protocol Safety Review Team (PSRT) meets twice monthly rather than biweekly.

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

To eliminate possible misunderstanding, "masked treatment group" has been removed from the first sentence in this section. The nature of data provided in DSMB reports is stated clearly in the final sentence in this section.

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

As instructions are not provided in the SSP regarding care and counseling provided by site staff for social harms experienced by study participants, reference to the SSP as a source of guidance for this activity has been removed from Section 10.6.

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

The URL for "Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials" has been updated.

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

In addition to the revisions pertaining to restriction of the study population to women in sub-Saharan Africa (summarized in Item 1S above), the following changes have been made to the *Sample informed consent form*.

A Clarification that VRC01 not on licensure path

At the request of the US FDA, a sentence has been added to Section 3 stating that the developer has no current plans to bring VRC01 to market.

B Risks of VRC01 updated

Per the revised Investigator's Brochure, new information has been added to "*Risks of VRC01 antibody*."

C Anaphylaxis and serum sickness specified

That the lists of symptoms in the first two bullets under *General risks of antibodies* apply to anaphylaxis and serum sickness has been clarified.

D Formatting revised in Section 6

To enhance continuity and clarity, what was formerly the first bullet has been incorporated into the header line and the bullet marking the remaining option has been removed.

E Site prompt revised in Section 7

For clarity, two site prompts in Section 7 concerning birth control, have been consolidated into a single prompt at the beginning of this section.

F Placebo is liquid clarified in Section 10

G Infusion procedure clarified in Section 11

The "IV" description in Section 11 has been revised to describe the intravenous infusion procedure more accurately. In addition, an instruction to contact the clinic staff with any concerns after getting an infusion has been added at the end of this section.

H STI testing clarified in Section 12

Description of STI testing in Section 12 has been revised (see Item 1O above).

I Procedures for participants who stop getting IVs for reasons other than HIV infection added as new Section 19

Description of the Schedule 4 procedures for participants whose infusions have been discontinued for reasons other than HIV infection has been added as Section 19 of Appendix A.

J Protection of private information relocated to Section 22

In order to keep consent form sections describing the study procedures contiguous, the section concerning protection of private information has been relocated to the end of "Being in the study."

K Risk of interference with future approved prevention approach removed from Section 23

Because this study product has not been shown to perturb the immune system and because it is known to be cleared from the body in a relatively short time, this warning, which is standard in consent forms for HVTN vaccine studies, has been removed from the list of "unknown risks" in Section 23.

L Minor wording changes in Appendix A

For ease of reading and enhanced comprehension, wording has been simplified in several locations in Appendix A. In these instances, the original meaning has been preserved.

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

More detailed information has been added about visit schedules and procedures for participants who are discovered to have been HIV-infected at enrollment or who become HIV-1 or HIV-2–infected while enrolled in the study. Sites are given two options for presenting this information:

- New Sections 17 and 18 in Appendix A (i.e., the main study consent), or
- Revised Section 16 in Appendix A and Appendix E (a new optional consent form specifically for participants diagnosed with HIV infection).

A site prompt above Section 16 in Appendix A instructs sites how to exercise each of these options.

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

Text in Sections 13 of Appendix A, *Sample informed consent form*, regarding sample testing, has been revised to more clearly describe what sorts of genetic testing participants' samples may be subject to. In addition, notation of genetic testing of HIV recovered from participant samples has been added.

Similar clarification has been added in Sections 14 and 27 of Appendix A and the corresponding Sections 9 and 13 of Appendix C, *Sample consent form for use of samples and information in other studies*.

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

Per MCC guidance, contact information for the MCC has been added to the contact list in the "Questions" of each consent form.

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

Injectable birth control has been added to the list of approved birth control drugs for preventing pregnancy. In addition, in parallel to "hysterectomy" being uterus removal, "oophorectomy" has been added as the formal name for ovary removal.

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

Consent form procedure tables have been added in Appendix D for:

- Participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected during the study;
- Participants who become HIV-1–infected; and
- Participants who discontinue infusions for reasons other than HIV infection.

In addition, STI testing has been added to the table of procedures for HIV-uninfected participants, along with a footnote indicating that STI testing may occur at other timepoints if clinically indicated.

A site prompt regarding how sites may present these procedures tables has been added to Appendix D. Similar prompts have been added to Sections 17, 18, and 19 of Appendix A.

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

Footnote 6 in Appendix F and footnote 5 in Appendix J have been revised to clarify that negative pregnancy test results must be obtained on the day of infusion prior to infusion.

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

The lists of endpoint laboratories in footnote 2 beneath each of the Laboratory procedures table have been divided into lists of laboratories affiliated with the HVTN Laboratory Program and non-HVTN laboratories.

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

Appendix F has been revised to show that assays for anti-VRC01 antibody levels may be performed at the NIAID Vaccine Research Center (VRC) lab or at NVITAL. Accordingly, the VRC has been added to the list of endpoint laboratories in Section 1 and has been added to the list of non-HVTN laboratories in the footnotes beneath the tables. Also NVITAL has been moved to the list of non-HVTN laboratories in Appendices F, G, and I.

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

The titles of Appendices G, H, K, and L have been revised to clarify to which categories of HIV-infected study participants each visit schedule applies. In addition, since both HVTN and HPTN sites will be participating in this study, reference to "HVTN" has been removed from the titles of Appendices K and L.

The visit schedule for HIV-infected study participants (ie, Schedule 2) has been revised to allow sufficient time to complete the activities required before the succeeding follow-up visits.

That assessment of HIV/AIDS-related conditions is part of both the complete and abbreviated physical exams has been clarified in Appendices K and L. In addition, "Social impact questionnaire" has been removed from these two schedules of procedures.

Finally, visit numbering has been revised in Appendices G, H, K, and L. The new numbering in Appendices G and K supersedes that implemented in Clarification Memo 1 to Version 1.0 of the protocol.

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

The protocol-specific HIV-1 diagnostic algorithm for this study includes potential DNA PCR testing, which requires whole blood. For this reason, an additional EDTA tube has been added to the blood drawn for confirmatory HIV testing (at Visit #.X) in Appendices G and H. In addition, an explanatory footnote regarding this additional blood draw has been added to each of these appendices.

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

Administration of a participant questionnaire was inadvertently inserted at the screening visit (Visit 0) in Appendix J. This has been removed.

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

For consistency with HVTN protocol conventions, local lab assessments have been added to the appendices listing the Schedule 2 and 3 procedures at CRS (ie, Appendices K and L).

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

Errors of grammar and in use of acronyms and abbreviations have been corrected. In addition, figures, tables, and appendices have been renumbered and cross-references have been updated 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: 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: Version 1.0
Protocol modification: Original protocol