



December 14, 2017

Full Protocol Amendment 3

A summary of changes to

Protocol

Version 4.0

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

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Item 1 Sample size increased from 1500 to 1900

The sample size is being increased in order to ensure 90% power to detect 60% prevention efficacy (PE) among women enrolled in HVTN 703/HPTN 081. This increase is based upon the early incidence data reported to the Data and Safety Monitoring Board (DSMB) in November 2017. The DSMB had no objections to increasing the sample size if the Study Team wanted to do so to increase power. This increase also will provide reasonable power to assess the critical secondary objective to identify correlates of protection, that is, developing marker(s) of the VRC01 monoclonal antibody that correlate with the level and antigenic specificity of protection against HIV-1, the trial sample size has been increased from 1500 to 1900. Having sufficient power to fully evaluate this secondary objective is critical to the future of monoclonal antibody studies in the HIV prevention field and for their contribution to the HIV vaccine field. Even with sufficient power to detect the target PE, moderate but clinically meaningful effect sizes in correlates analyses may nevertheless be missed. This increase in sample size will reduce the sensitivity of correlates analyses to fluctuations in endpoint event rates. In addition, while pooling across the AMP trials—HVTN 703/HPTN 081 among South African women at risk of heterosexual HIV-1 acquisition and HVTN 704/HPTN 085 among men who have sex with men (MSM) and transgender persons—increases overall power to assess the primary endpoint of preventive efficacy, this sample size increase helps increase the capacity to determine whether preventive efficacy and correlates of protection differ between the study population in the two trials.

We note that safety data to date indicate no increased risk to study participants (see the Chair/Medical Officer report Executive Summary dated 08 November 2017). We note further that Data and Safety Monitoring Board (DSMB) reviews, most recently in November 2017, have consistently expressed satisfaction with trial safety and conduct, including retention of study participants.

A Sample size revised in Section 1, Overview

Total and group sample sizes have been revised in *Table 1: Schema and Participants* in Section 1.

B Sample size revised in Section 2.4.1, *Cohort selection*

The total sample size has been revised in the first sentence in Section 2.4.1.

C Updated in Section 4.4.1, *Assumptions of the sample size calculations including sequential monitoring for PE*

The duration of participant accrual has been updated in the second bullet and the assumed annual control group HIV-1 incidence rate has been revised in the fourth bullet in Section 4.4.1. In the last paragraph in this section, the lower incidence rate accounting for increased PrEP usage has been revised. References to increased dropout rates have been removed.

D Updated in Section 4.4.2, *Power curves and operating characteristics of the design (Primary objective 2)*

The second paragraph in Section 4.4.2, Figure 4-1, and Table 4-1 have been updated to reflect the revised sample size and incidence assumptions noted in Section 4.4.1. In addition the first sentence in the second paragraph has been corrected to more accurately describe Figure 4-1 and the estimated sample size needed to achieve 90% power to detect PE = 60% has been updated.

E Updated in Section 4.4.3, *Additional operating characteristics of the design for assessing primary objective 2*

The sample size, “lower incidence”, and power have been updated in the text of Section 4.4.3. Figure 4-2 has been updated. Reference to the projected dropout rate in the text and the Figure 5-3 caption has been removed.

F Updated in Section 4.4.4, *Additional operating characteristics of the primary analysis accounting for the sequential monitoring*

The total sample size has been updated in the first sentence of Section 4.4.4. The number of control and mAb recipients has been updated in captions to Figure 4-3 and Table 4-2. Figure 4-3, Table 4-2, and Table 4-3 have been updated accordingly.

G Updated in Section 4.4.5, *Power curves for secondary hypothesis tests about PE in each mAb group*

Figure 4-4 has been updated. Reference to a higher than expected dropout rate has been removed from the caption.

H Updated in Section 4.4.6, *Rationale for the HIV-1 incidence assumptions*

The assumed background incidence rate has been updated in the first sentence in Section 4.4.6. Reference to the ASPIRE study has been added and that to the CAPRISA 004 study has been removed. The second paragraph has been revised to

reflect the changed incidence assumptions. Calculations of incidence under different conditions of PrEP usage have been revised in the third paragraph.

I Updated 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*

Table 4-4 has been updated in Section 4.5, as has the characterization of large and moderate differences in prevention efficacy (PE) and the calculations of power to detect these differences.

J Updated in Section 4.6, *Sample size calculations for safety*

Group sizes have been revised in the first two paragraphs in Section 4.6. Confidence intervals around event rates have been updated in Table 4-5. Reference to the method by which these confidence intervals are calculated has been updated in the footnote to Table 4-5 as had the corresponding literature reference (recorded as reference 119 in Section 17). Figure 4-5 has been updated. In the final paragraph, the true SAE rates associated with 80% and 90% power to detect a higher SAE rate in a mAb arm have been updated.

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

The total sample size has been updated in the captions to Figures 4-8 and 4-9. In addition, because the power calculations in those figures depend only on the projected number of endpoint events and not on sample size, reference to “Total Sample Size” has been removed from these figures.

L Sample size revised in Appendix A, *Sample informed consent form*

The sample size has been revised in the first sentence in the second paragraph of *About the study* in Appendix A.

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

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

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: December 14, 2017

Protocol version: Version 4.0

Protocol modification: Full Protocol Amendment 3

- Item 1 Sample size increased from 1500 to 1900
- Item 2 Added in Appendices A and C: Broad regulatory agency access to participant study records

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 fertility 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