



July 19, 2016

Full Protocol Amendment 1

**A summary of changes to
Protocol**

Version 2.0

HVTN 704/HPTN 085

**A phase 2b study to evaluate the safety and efficacy of
VRC01 broadly neutralizing monoclonal antibody in reducing
acquisition of HIV-1 infection among men and transgender
persons who have sex with men**

DAIDS-ES ID 30095

IND 113,611 HELD BY DAIDS

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

The following information impacts the HVTN 704/HPTN 085 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) and any other applicable Regulatory Entity (RE) as soon as possible for their information and review. Their approval is required before implementation.

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

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

Upon receiving final IRB/EC and any other applicable RE approval(s), sites are required to submit an amendment registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a Registration Notification for the amendment once the DAIDS PRO verifies that all the required amendment registration documents have been received and are complete. A Registration Notification from the DAIDS PRO is 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.

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Item 1 Corrected in Section 1, Overview: Estimated total study duration

An error in calculating the estimated total study duration has been rectified, increasing the estimated study duration from 56 to 59 months.

Item 2 Added: Switzerland as study location

Notation that this study will be conducted in Switzerland as well as at sites in North and South America has been added in the following locations:

- Section 1, *Overview*, under “Participants”
- Section 2.4.1, *Cohort selection*
- Section 2.5.3, *Operationalizing PrEP access*
- Section 4.6.3, *Additional operating characteristics of the design for assessing primary objective 2*
- Section 4.6.6, *Rationale for the HIV-1 incidence assumptions*
- Section 13, *IRB/EC/RE review considerations*
- Appendix A, *Sample informed consent form*

In addition, a sentence describing the proportion of new HIV infections in the US, Latin America, and Switzerland attributed to MSM has been added to Section 2.4.1 along with supporting references.

Item 3 Added in Section 1 and Appendices F through I: HIV diagnostic laboratories in Peru and Brazil

Laboratories have been established in Peru and Brazil to provide diagnostic HIV testing for participants in HVTN 703/HPTN 081. These have been added to the list of endpoint laboratories in Section 1, *Overview*, in the “Ship to” and “Assay location” columns for HIV diagnostics in the laboratory procedures tables in Appendices F through I, and in footnote 2 beneath each table. The previous generic designation “Regional Network HIV Diagnostic Laboratories in South America” has been removed from these locations.

Item 4 Updated in Section 1.1: *Protocol team membership*

The Protocol Team list has been updated per staffing changes and updated position titles.

Item 5 Revised: PrEP monitoring

In order to more accurately and comprehensively monitor PrEP uptake and to control for this factor in the analysis of VRC01 efficacy in preventing HIV infection, the primary method for laboratory monitoring of PrEP use has been changed from a broad qualitative ARV screen to a more focused semi-quantitative TDF assay using dried blood spots. In addition, dried blood spots will be obtained from all participants at all scheduled study visits to facilitate their inclusion in case-control analyses. This shift in approach is reflected in the following protocol changes.

A ARV monitoring technology description removed from Section 2.5.3, *Operationalizing PrEP access*

Reference to “high throughput mass spectrometry” has been removed and a cross-reference to Section 4.10 has been added.

B Revised in Section 3.3, *Exploratory objectives*

Exploratory objectives 1 and 2 have been revised to reflect the fact that dried blood spot method being adopted for PrEP monitoring tests for FTC/TDF use but not for other ARVs.

C Monitoring of ARV use revised in Section 4.10, *Assessment of PrEP use*

The title of this section has been revised to reflect a focus on PrEP uptake rather than broad screening for ARV use. Text describing possible methods of monitoring ARV use has been replaced with description of dried blood spot sampling for evaluation of tenofovir metabolite concentrations in red blood cells using a calendar-based selection of visits. This section also now includes reference to the study monitoring plan, a non-protocol document. Clarification that reports of ARV drug use will be provided to the DSMB and the Oversight Committee, and that the protocol team leadership will see treatment-pooled ARV drug use summaries has been added as well.

D Notation of blood to be collected for PrEP monitoring added in Sections 7.3, 7.4, and 7.7

Notation that blood samples are being collected for PrEP monitoring has been added to the sample collection bullet in each of the listed sections.

E 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 mass spectrometry analysis with assessment of intracellular levels of tenofovir diphosphate, a TDF metabolite, in red blood cells recovered from dried blood spots. Because this assay provides more information about regularity of FTC/TDF use over a longer period of time, it supports more precise estimation of PrEP use in the study population and potential PrEP impacts on HIV incidence and endpoint accrual.

F Revised in Appendix F, Schedule 1—Laboratory procedures for HIV-uninfected participants

The table of laboratory procedures in Appendix F has been revised to reflect collection of dried blood spots from all study participants at all scheduled study visits, while retaining the option of ARV detection by serum or plasma. These changes include:

- addition of a row labeled “ARV detection by dried blood spots” with a 2mL EDTA tube specified at each study visit, CSR specified as the “ship to” and UC Denver as the “assay location”, and addition of footnote 10;
- revision of “ARV detection” to “ARV detection by serum or plasma” and addition of footnotes 9 and 10;
- addition of University of Colorado, Denver to the list of non-HVTN endpoint labs in footnote 2 in Appendix F and in Section 1, *Overview*; and
- addition of these blood draws to the 56-day and overall blood draw totals.

G Revised in Appendix I, Schedule 4—Laboratory procedures for participants who discontinue infusions for reasons other than HIV infection

As these participants will be included in MITT analyses of VRC01 efficacy, PrEP monitoring has been added to the schedule for participants who discontinue infusions for reasons other than HIV infection. As a consequence, the following changes have been made to the Schedule 4 table of laboratory procedures:

- changing a subhead in the table from “Drug Levels” to “Drug Levels/Detection”;
- adding a row for “ARV detection by serum or plasma” with Ship to “CSR” and “JHU” Assay location and footnote 8 indicating that EDTA blood collected for plasma may also be used for ARV detection if necessary;
- adding a row for “ARV detection by dried blood spots” with Ship to “CSR” and “UC Denver” as Assay location, footnote 9, and a 2mL EDTA tube collected at each scheduled visit;
- addition of the JHU and UC Denver labs to the list of non-HVTN laboratories in footnote 2; and
- addition of these blood draws to the 56-day and overall blood draw totals.

Item 6 Removed in Section 2.9.3, HVTN 104: Incorrect systemic reactogenicity rate

Two sentences in the third paragraph in Section 2.9.3 pointed to differing proportions of participants displaying systemic reactogenicity symptoms. The first of the two sentences is correct. The second sentence has been removed.

Item 7 Clarified in Sections 4.9.1 and 10.4.3: Data reporting to DSMB

Because the DSMB has the option of reviewing fully unblinded study data or reviewing data by coded group, specification that the DSMB will review “unblinded study data” has been removed from the first paragraph in Section 4.9.1. Similarly, to avoid misunderstanding, “masked treatment group” has been removed from the first sentence in Section 10.4.3. The nature of data provided in DSMB reports is stated clearly in the final sentence in this section.

Item 8 Clarified in Section 4.9.1.1, *Sequential monitoring for potential harm, non-efficacy, and high efficacy*: Caption to Figure 4-6

The caption to Figure 4-6 has been revised for consistency with the footnote to Table 4-6.

Item 9 Added in Section 5.1, *Inclusion criteria*: Reference to SSP for clarification of transgender eligibility

Reference to the Study Specific Procedures has been added to this section for more details regarding inclusion criterion #9, especially with regard to determining the eligibility of transgender persons.

Item 10 Clarified in Section 5.2, *Exclusion criteria*: PSRT may permit exceptions to Exclusion criterion #4

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

Item 11 Clarified in Section 6, *Study product preparation and administration*: Administration volumes, bag covers, and expiration prompts**A Administration volumes clarified**

In order to account for normal variation in the volume of study product solution and to clarify that the entire bag contents should be administered, treatment descriptions in Section 6.1 have been revised to indicate that 150mL is the target volume for preparation of study products in the pharmacy and the final paragraph in Section 6.4 has been revised to specify administration of the entire contents of the study product solution; specification that the volume to be administered is 150 mL has been removed.

B Bag covers added to ensure blinding

In order to ensure blinding between groups, instructions to pharmacists to place a bag cover over the bag and to clinic staff not to remove it have been added to Sections 6.3.1, 6.3.2, and 6.3.3.

C Notes concerning study product expiration clarified

Text has been revised in the italicized notes in Sections 6.3.1, 6.3.2, and 6.3.3 to more clearly convey to pharmacists that institutional policies regarding study product expiration take precedence if these are more stringent than the timeframes shown in the protocol.

Item 12 Removed in Section 7.2, *Pre-enrollment procedures*: Required recording of generic names for concomitant medications

For recording concomitant medications, both trade names and generic names are allowed; hence, parenthetical language requiring recording of the complete generic name for all concomitant medications has been removed.

Item 13 Clarified in Section 7.3, *Enrollment and infusion visits* and Section 7.10, *Assessment of reactogenicity*: Recording and source documentation for reactogenicity events

Text in the cited sections has been revised clarify the process by which clinic staff obtain information on reactogenicity events and how those events are recorded on source documents. Reference to the Study Specific Procedures for more detailed information has been added in Section 7.10.

Item 14 Clarified in Section 7.3, *Enrollment and infusion visits*, and Appendices D, F, and J: STI testing

For consistency with Appendix F, *Schedule 1—Laboratory procedures for HIV-uninfected participants*, Section 7.3, *Enrollment and infusion visits*, has been revised to indicate that gonorrhea testing will also be conducted using oropharyngeal swabs. Footnote 12 to Appendix F, *Schedule 1—Laboratory procedures for HIV-uninfected participants*, has been revised to clarify that nucleic acid amplification testing (NAAT) will be used for all urine and rectal/oropharyngeal swab samples. In addition, footnote 14 to Appendix F and footnote 8 to Appendix J, *Schedule 1—Procedures at CRS for HIV-uninfected participants*, have been revised to clarify that combination gonorrhea/chlamydia tests may be used for oropharyngeal swabs. Reference to the SSP for results reporting has been added to this footnote as well. In the footnotes, additional STI testing “if indicated by symptoms” has been revised to “if clinically indicated.” This change has also been made in the last footnote to the first table in Appendix D.

Item 15 Clarified in Section 7.9, *Urine testing*: Follow-up to abnormal urine dipstick result at screening

The second paragraph in Section 7.9 has been revised to clarify follow-up for a transiently abnormal and exclusionary urine dipstick result at screening. A sentence has been added to the final paragraph instructing site staff to document abnormal follow-up urine dipstick due to infection and to provide appropriate treatment and/or referral.

Item 16 Clarified in Appendix A, *Sample informed consent form*: VRC01 not being developed for sale

At the request of FDA, language has been added to the third paragraph in Section 3 indicating that VRC01 is not being developed with the intention of marketing.

Item 17 Added in Appendix A, *Sample informed consent form*: Option to include consent for HIV-infected study participants

In Version 1.0 of the protocol, the sample consent form for study participants who become HIV-infected or who are discovered to have been HIV-infected at enrollment was included as Appendix E, *Sample consent form for participants with HIV infection at enrollment or during the study*. It was anticipated that this form, which outlines the schedules of visits and procedures for HIV-infected participants, would be presented to study participants upon confirmation of HIV infection. In response to input from staff at some clinical sites, Appendix A, *Sample informed consent form*, has been revised to include the option of presenting this information in the primary consent form for the study. Hence, site staff may now obtain consent for participation in Schedules 2 and 3 by including in their site-specific consent forms either:

- Highlighted Sections 17 and 18 in Appendix A, or
- Section 16 in Appendix A and Appendix E.

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

Item 18 Renumbered in Appendix A: Section 19, “If you stop getting IVs for reasons other than HIV infection...”

The cited section has been relocated in order to make contiguous all consent sections concerning participant visit schedules and procedures.

Item 19 Added in Appendix D: Procedure tables for HIV-infected participants and for participants whose infusions have been stopped for reasons other than HIV infection

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; and
- Participants who become HIV-1–infected.

A site prompt describing how sites may present these procedures tables has been added to Appendix D and corresponding site prompts have been inserted into Appendix A.

Item 20 Clarified in Appendix E, *Sample consent form for participants with HIV infection at enrollment or during the study*: Number of visits, physical exams, and HIV transmission risk counseling**A Number of visits clarified**

Since the consent form specifically for HIV-infected study participants will most likely be administered after confirmation of HIV infection has been received at the site, the number of

additional clinic visits a participant will be asked to make has been adjusted throughout this sample form.

B Clarification of physical exams

For consistency with Section 2, the second bullet in Section 1 has been revised to indicate that exams will be based on “your complaints or symptoms.”

C Clarification of transmission avoidance counseling

Language has been clarified in the bullets on counseling to avoid HIV transmission.

Item 21 Throughout protocol document: Minor errors corrected

Minor typographical errors have been corrected throughout the protocol document. In addition, the acronym list in Section 16 has been updated.

Item 22 Updated: Section 14, *Version history*

Protocol modifications are made to HVTN protocols via clarification memos, letters of amendment, or full protocol amendments. HVTN protocols are modified and distributed according to the standard HVTN procedures as described in the HVTN Manual of Operations (MOP).

The version history of, and modifications to, Protocol HVTN 704/HPTN 085 are described below.

Date: July 19, 2016

Protocol version: Version 2.0

Protocol modification: Full Protocol Amendment 1

- Item 1 Corrected in Section 1, *Overview*: Estimated total study duration
- Item 2 Added: Switzerland as study location
- Item 3 Added in Section 1 and Appendices F through I: HIV diagnostic laboratories in Peru and Brazil
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- Item 17 Added in Appendix A, *Sample informed consent form*: Option to include consent for HIV-infected study participants
- Item 18 Renumbered in Appendix A: Section 19, “If you stop getting IVs for reasons other than HIV infection...”

- Item 19 Added in Appendix D: Procedure tables for HIV-infected participants and for participants whose infusions have been stopped for reasons other than HIV infection
- Item 20 Clarified in Appendix E, *Sample consent form for participants with HIV infection at enrollment or during the study*: Number of visits, physical exams, and HIV transmission risk counseling
- Item 21 Throughout protocol document: Minor errors corrected
- Item 22 Updated: Section 14, *Version history*

Date: March 9, 2016

Protocol version: 1.0

Protocol modification: NA (Original protocol)