

December 14, 2016

Letter of Amendment 1

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.

Upon receiving final IRB/EC and any other applicable Regulatory Entity (RE) approval(s) for this LoA, sites should implement the LoA immediately.

Upon receiving final IRB/EC and any other applicable RE approvals, sites are required to submit a Letter of Amendment (LOA) registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a Registration Notification for the LOA once the DAIDS PRO verifies that all the required LOA registration documents have been received and are complete. A Registration Notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the Registration Notification along with this letter of amendment and any IRB/EC correspondence should be retained in the site's regulatory files.

For additional information on the registration process and specific documents required for LOA registration, refer to the current version of the DAIDS Protocol Registration Manual.

The following information may also affect the sample informed consent. Your IRB/EC will be responsible for determining the process of informing study participants of the contents of this letter of amendment.

List of changes

Item 1	Revised in Section 1, <i>Overview</i> and Section 4.9.1, <i>Role of the Data Safety Monitoring Board (DSMB): Interim safety assessments</i>	2
Item 2	Revised in Section 2.4.5, <i>Trial monitoring: Feasibility assessment</i>	3

The changes described herein will be incorporated in the next version of Protocol HVTN 704/HPTN 085 if it undergoes full protocol amendment at a later time.

Item 1 Revised in Section 1, *Overview* and Section 4.9.1, *Role of the Data Safety Monitoring Board (DSMB): Interim safety assessments*

Cumulative safety data with multiple administrations of the VRC01 monoclonal antibody across several clinical trials has been reassuring to date. Given the close ongoing safety oversight provided by medical monitors and the Protocol Safety Review Team and regular evaluations of participant safety (blinded and unblinded) by the Data Safety Monitoring Board (see protocol sections 4.9.1.1 and 10), restricting enrollment prior to completion of the protocol-specified interim safety assessment has been deemed unnecessary and has been removed. An earlier review of interim safety data requested by the US FDA has been added.

A Revised in Section 1, *Overview*

Previous and revised texts for the note below Table 1-1 are shown below.

Previous:

An interim safety assessment will be performed through the Week 24 visit for the first 450 enrolled participants. This number may include participants enrolled in the run-in in sister study HVTN 703/HPTN 081. Infusions for those 450 participants will continue while the interim safety assessment is conducted. Following enrollment of the 450th participant, enrollment can continue, subject to the following condition: No more than 25% of the total study population may be enrolled before the interim safety report is complete, reviewed by the DSMB, and submitted to the US FDA. Enrollment will then continue only if the safety record for the run-in subgroup is deemed satisfactory.

Revised:

Interim safety assessments will be performed for participants who reach the Week 16 visit by November 19, 2016 and also through the Week 24 visit for the first 450 enrolled participants. Infusions and enrollment will continue while these interim safety assessments are conducted. The interim safety reports will be submitted to the DSMB and to the US FDA.

B Removed in Section 4.9.1, *Role of the Data Safety Monitoring Board (DSMB)*

The final paragraph in Section 4.9.1 regarding capping enrollment during interim safety assessment, has been removed, as indicated below.

Deleted:

Moreover, as described in Section 1, the safety run-in cohort includes up to 675 enrolled participants, with an enrollment pause, if necessary, after the 675th enrolled participant. Once the 450th enrolled participant (possibly including participants in the safety run-in in sister study HPTN 703/HPTN 081) reaches the Week 24 study visit, a comprehensive safety report is compiled and provided to the DSMB. If the safety data are deemed satisfactory, then enrollment would recommence (or continue).

Item 2 Revised in Section 2.4.5, *Trial monitoring: Feasibility assessment*

Given ongoing monitoring of expected vs. actual study visit completion, participant retention, the number of missed infusions, and the number of participants for whom infusions have been permanently discontinued, and recent DSMB review of these numbers and recommendation that enrollment should continue, restriction on enrollment pending completion of the early feasibility assessment has been deemed unnecessary and has been removed (deleted text shown by ~~striketrough~~).

Revised:

As this is the first large-scale phase 2b study with IV administration of a biomedical intervention for prevention of sexual HIV-1 transmission, the trial design includes an early feasibility check. After approximately 120 participants have completed the Week 32 visit, a treatment-blinded analysis of infusion feasibility will be conducted and reported to the DSMB. Enrollment of the remaining study participants will be deemed feasible if $\geq 80\%$ of those 120 participants remain engaged in the trial and have not declined further infusions. Enrollment will not be paused for this feasibility assessment, ~~with the condition that no more than approximately 25% of the planned full study population will be enrolled prior to completion of the assessment.~~

Protocol modification history

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

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

Date: December 14, 2016

Protocol version: Version 2.0

Protocol modification: Letter of Amendment 1

- Item 1 Revised in Section 1, *Overview* and Section 4.9.1, *Role of the Data Safety Monitoring Board (DSMB)*: Interim safety assessments
- Item 2 Revised in Section 2.4.5, *Trial monitoring*: Feasibility assessment

Date: July 19, 2016

Protocol version: Version 2.0

Protocol modification: Full Protocol Amendment 1

- Item 1 Corrected in Section 1, *Overview*: Estimated total study duration
- Item 2 Added: Switzerland as study location
- Item 3 Added in Section 1 and Appendices F through I: HIV diagnostic laboratories in Peru and Brazil
- Item 4 Updated in Section 1.1: *Protocol team* membership
- Item 5 Revised: PrEP monitoring
- Item 6 Removed in Section 2.9.3, *HVTN 104*: Incorrect systemic reactogenicity rate
- Item 7 Clarified in Sections 4.9.1 and 10.4.3: Data reporting to DSMB
- Item 8 Clarified in Section 4.9.1.1, *Sequential monitoring for potential harm, non-efficacy, and high efficacy*: Caption to Figure 4-6
- Item 9 Added in Section 5.1, *Inclusion criteria*: Reference to SSP for clarification of transgender eligibility
- Item 10 Clarified in Section 5.2, *Exclusion criteria*: PSRT may permit exceptions to Exclusion criterion #4
- Item 11 Clarified in Section 6, *Study product preparation and administration*: Administration volumes, bag covers, and expiration prompts
- Item 12 Removed in Section 7.2, *Pre-enrollment procedures*: Required recording of generic names for concomitant medications
- Item 13 Clarified in Section 7.3, *Enrollment and infusion visits* and Section 7.10, *Assessment of reactogenicity*: Recording and source documentation for reactogenicity events
- Item 14 Clarified in Section 7.3, *Enrollment and infusion visits*, and Appendices D, F, and J: STI testing

- Item 15 Clarified in Section 7.9, *Urine testing*: Follow-up to abnormal urine dipstick result at screening
- Item 16 Clarified in Appendix A, *Sample informed consent form*: VRC01 not being developed for sale
- Item 17 Added in Appendix A, *Sample informed consent form*: Option to include consent for HIV-infected study participants
- Item 18 Renumbered in Appendix A: Section 19, “If you stop getting IVs for reasons other than HIV infection...”
- Item 19 Added in Appendix D: Procedure tables for HIV-infected participants and for participants whose infusions have been stopped for reasons other than HIV infection
- Item 20 Clarified in Appendix E, *Sample consent form for participants with HIV infection at enrollment or during the study*: Number of visits, physical exams, and HIV transmission risk counseling
- Item 21 Throughout protocol document: Minor errors corrected
- Item 22 Updated: Section 14, *Version history*

Date: March 9, 2016

Protocol version: Version 1.0

Protocol modification: Original protocol