



November 9, 2017

Clarification Memo 1

Version 3.0

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

[BB 113,611—HELD BY DAIDS]

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

Please distribute this clarification memo to all appropriate staff members, and file with your protocol documents. Consult your local Institutional Review Board (IRB)/Ethics Committee (EC) regarding submission requirements for clarification memos.

List of changes

- Item 1 Clarified in Section 6, *Study product preparation and administration: Sodium Chloride for Injection USP, 0.9% containers and volumes*2

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 Clarified in Section 6, Study product preparation and administration: Sodium Chloride for Injection USP, 0.9% containers and volumes

Language in this section has been revised to clarify that Sodium Chloride for Injection USP, 0.9% may be obtained from and infusions may be prepared in containers other than 100 mL IV bags. In addition, clarification is added that, for the duration of the critical shortage, Sodium Chloride for Injection USP, 0.9% may be provided to clinical research sites through the study. Revised text is shown below (deletions shown by ~~double strikethrough~~; added text in **bold underline**).

A Revised in Section 6.3, Preparation of study products**Revised:****6.3.1 VRC-HIVMAB060-00-AB (10mg/kg IV) - (Group 1)**

To prepare an IV infusion, the pharmacist will calculate the dose [total milligrams needed ($10 \text{ mg/kg} \times \text{participant's weight in kg}$)] and remove the total number of vials needed as well as a 100 mL IV bag **or IV glass bottle** of Sodium Chloride for Injection USP, 0.9% **(NSS)** from storage. **Alternatively, the pharmacist can obtain a different volume of NSS in an IV bag or IV glass bottle (50 mL, 150 mL, 200 mL, 250 mL, 500 mL, or other sizes as available up to 500 mL) for use to prepare the study IV infusion.** If the product has been stored at 2°C to 8°C, the vials should be equilibrated to room temperature for 30 minutes and may be held at **controlled** room temperature (~~not to exceed~~ **maximum** 27°C) for up to 8 hours prior to product preparation. The pharmacist will also calculate the additional amount of Sodium Chloride for Injection USP, 0.9% needed to prepare a final total volume of 150 mL and remove this from storage.

Prior to preparation, the pharmacist should gently swirl the vials containing VRC01 and then inspect for particles. DO NOT SHAKE VIALS. If visible particles are present, the product will not be used (see Section 6.2 for more information). The pharmacist, using aseptic technique, will add the appropriate amount of Sodium Chloride for Injection USP, 0.9% to the 100 mL IV bag **or IV glass bottle** of Sodium Chloride for Injection USP, 0.9%. The pharmacist, still using aseptic technique will add the appropriate volume of VRC01 to that same **IV bag or IV glass bottle** for a final total volume of 150 mL. **Alternatively, if the pharmacist is using a different size IV bag or IV glass bottle containing NSS, please refer to the Study Products Considerations section of the SSP for further preparation instructions.** The IV bag **or IV glass bottle** will be labeled as “VRC01 or Control in Normal Saline Total Volume = 150 mL”. The weight used for calculating the dose should be written on the label. A bag cover will be placed over the **IV bag or IV glass bottle** and should not be removed by the clinic staff. The IV bag **or IV glass bottle** will be labeled with a DO NOT INFUSE after date and time as follows:

- 24 hours if stored at 2°C to 8°C

- 8 hours, including completion of infusion, if stored at controlled room temperature (~~not to exceed 30~~ **maximum 27°C**)

Product may NOT be stored in direct sunlight.

Note: Site pharmacists must follow their institutional policies for expiration dates (ie, DO NOT INFUSE after date and time), if shorter than timeframes above.

Any empty vials, unused portion of entered vials, or unused IV solution that contains study product should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

6.3.2 VRC-HIVMAB060-00-AB (30mg/kg IV) - (Group 2)

To prepare an IV infusion, the pharmacist will calculate the dose [total milligrams needed ($30 \text{ mg/kg} \times \text{participant's weight in kg}$)] and remove the total number of vials needed as well as a 100 mL IV bag **or IV glass bottle** of Sodium Chloride for Injection USP, 0.9% (NSS) from storage. **Alternatively, the pharmacist can obtain a different volume of NSS in IV bag or IV glass bottle (50 mL, 150 mL, 200 mL, 250 mL, 500 mL, or other sizes as available up to 500 mL) for use to prepare the study IV infusion.** If the product has been stored at 2°C to 8°C, the vials should be equilibrated to room temperature for 30 minutes and may be held at **controlled** room temperature (~~not to exceed~~ **maximum 27°C**) for 8 hours prior to product preparation. The pharmacist will also calculate the additional amount of Sodium Chloride for Injection USP, 0.9% needed to prepare a final total volume of 150 mL and remove this from storage.

Prior to preparation, the pharmacist should gently swirl the vials containing VRC01 and then inspect for particles. DO NOT SHAKE VIALS. If visible particles are present, the product will not be used (see Section 6.2 for more information). The pharmacist, using aseptic technique, will add the appropriate amount of Sodium Chloride for Injection USP, 0.9% to the 100 mL IV bag **or IV glass bottle** of Sodium Chloride for Injection USP, 0.9%. The pharmacist, still using aseptic technique will then add the appropriate volume of VRC01 to that same **IV bag or IV glass bottle** for a final total volume of 150 mL. **Alternatively, if the pharmacist is using a different size IV bag or IV glass bottle containing NSS, please refer to the Study Products Considerations section of the SSP for further preparation instructions.** The IV bag **or IV glass bottle** will be labeled as “VRC01 or Control in Normal Saline Total Volume = 150 mL”. The weight used for calculating the dose should be written on the label. A bag cover will be placed over the **IV bag or IV glass bottle** and should not be removed by the clinic staff. The IV bag **or IV glass bottle** will be labeled with a DO NOT INFUSE after date and time as follows:

- 24 hours if stored at 2°C to 8°C
- 8 hours, including completion of infusion, if stored at controlled room temperature (not to exceed 30°C)

Product may NOT be stored in direct sunlight.

Note: Site pharmacists must follow their institutional policies for expiration dates (ie, DO NOT INFUSE after date and time), if shorter than timeframes above.

Any empty vials, unused portion of entered vials, or unused IV solution that contains study product should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

6.3.3 Control for VRC01 (Group 3)

To prepare an IV infusion, the pharmacist, using aseptic technique, will add 50 mL of Sodium Chloride for Injection USP, 0.9% to a 100 mL **IV bag or IV glass bottle** of Sodium Chloride for Injection USP, 0.9%. **Alternatively, the pharmacist can obtain a different volume of NSS in IV bag or IV glass bottle (50mL, 150 mL, 200 mL, 250 mL, or 500 mL) for use to prepare the study IV infusion. If the pharmacist is using a different size IV bag or IV glass bottle containing NSS, please refer to the Study Products Considerations section of the SSP for further preparation instructions.** The IV bag **or IV glass bottle** will be labeled as “VRC01 or Control in Normal Saline-Total Volume = 150 mL”. The weight used for calculating the dose should be written on the label. A bag cover will be placed over the **IV bag or IV glass bottle** and should not be removed by the clinic staff. The IV bag **or IV glass bottle** will be labeled with a DO NOT INFUSE after date and time as follows:

- 24 hours if stored at 2°C to 8°C
- 8 hours, including completion of infusion, if stored at controlled room temperature (~~not to exceed 30~~ **maximum 27°C**)

Product may NOT be stored in direct sunlight.

Note: Site pharmacists must follow their institutional policies for expiration dates (ie, DO NOT INFUSE after date and time), if shorter than timeframes above.

B Revised in Section 6.4, Administration

Revised:

6.4 Administration

VRC01 or Control (Intravenously)

Prior to infusion, if the VRC01 or Control IV bag **or IV glass bottle** has been stored at 2°C to 8°C, the **IV bag or IV glass bottle** must be equilibrated to room temperature (maximum of 30°C) for 30 minutes or longer and may be held for up to 8 hours, including equilibration time and completion of product administration. (NOTE: This 8 hour period may NOT exceed the DO NOT INFUSE after date and time on the IV bag **or IV glass bottle** label.)

The IV bag **or IV glass bottle** prepared by the pharmacy will include the weight that was used for preparation of the IV bag **or IV glass bottle** (VRC01 or Control). The clinician responsible for administration will check the **IV bag or IV glass bottle** label and confirm that the participant identifier is correct and that the weight on the **IV bag or IV glass bottle** label is within 10% of the participant's current actual weight (refer to Section 6.3 for more information).

An in-line filter infusion set must be used for IV administration (see SSP for specifications and additional details).

The entire contents of the investigational study product solution will typically be administered IV over about 15 to 60 minutes using a volumetric pump. The total time needed to administer the dose may be longer based on factors such as participant tolerance.

C Revised in Section 6.5, *Acquisition of study products*

6.5 Acquisition of study products

VRC-HIVMAB060-00-AB is provided by the VRC/DAIDS/NIAID.

~~Control for VRC01 (Sodium Chloride for Injection USP, 0.9%) will not be provided through the study during the NSS critical shortage period protocol and must be obtained by the site.~~ **should be obtained by the site or may**

Once a CRS is protocol registered, the pharmacist can obtain study products from the CRPMC by following the ordering procedures given in Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

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: November 9, 2017

Protocol version: Version 3.0

Protocol modification: Clarification Memo 1

- Item 1 Clarified in Section 6, *Study product preparation and administration*: Sodium Chloride for Injection USP, 0.9% containers and volumes

Date: August 29, 2017

Protocol version: Version 3.0

Protocol modification: Letter of Amendment 1

- Item 1 Updated in Section 2.9.5, *Particle formation*, and Section 6.2, *Study product formulation*: Product description and formulation/handling instructions
- Item 2 Revised in Section 4.9.3, *Monitoring for futility to assess PE*: Futility to assess PE monitoring targets
- Item 3 Clarified in Section 5, *Selection and withdrawal of participants*: Eligibility determination
- Item 4 Updated: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events
- Item 5 Corrected in Appendix D, *Tables of procedures (for sample informed consent form)*: Procedures at week 80 for HIV-uninfected participants
- Item 6 Clarified in Appendices F through I: Assay locations, discard tubes not required, and blood draw totals
- Item 7 Added in Appendix M, *Schedule 4—Procedures at CRS for participants who discontinue infusions for reasons other than HIV infection*: Participant unblinding
- Item 8 Added in Appendix J and M: Post-study confirmation of final HIV test results

Date: June 15, 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 Updated in Sections 2.9, 2.9.3, 2.9.4, and Appendix A: VRC01 clinical experience in HVTN 104
- Item 4 Revised in Section 4.9.3: *Monitoring for fertility to assess PE*
- Item 5 Clarified in Section 5.1, *Inclusion criteria*: Transgender volunteer eligibility
- Item 6 Added in Section 5.1, *Inclusion criteria*: Hgb criterion adjustment for MTF transgender volunteers using feminizing hormones
- Item 7 Clarified in Section 5.2, *Exclusion criteria*: Tissue or organ transplantation exclusion criterion
- Item 8 Updated in Section 6.2, *Study product formulation*: VRC01 description and storage temperature
- Item 9 Revised in Sections 6.3 and 6.4: Holding times for study products after preparation
- Item 10 Updated in Section 6.4 and Appendix A: Minimum infusion time
- Item 11 Added in Section 6.4, *Administration*: In-line filter set requirement
- Item 12 Clarified in Section 6.4, *Administration*: IV bag temperature equilibration and label weight
- Item 13 Clarified in Section 7.3, *Enrollment and infusion visits*: Timing of HIV infection assessment and HIV testing
- Item 14 Updated in Section 7.10, *Assessments of reactogenicity*, and Section 10.2.2, *AE reporting*: DAIDS AE grading table version and exceptions
- Item 15 Updated in Section 10.2, *Safety reporting*: URLs for referenced documents
- Item 16 Clarified in Section 10.2.2, *AE reporting*: Working hours for CSS or RML response
- Item 17 Updated in Section 10.2.3: *Expedited reporting of adverse events to DAIDS*
- Item 18 Updated in Section 14: Version history
- Item 19 Updated in Section 15, *Document references (other than literature citations)*: Documents and URLs
- Item 20 Corrected in Section 16: *Acronyms and abbreviations*
- Item 21 Corrected in Appendix A, *Sample informed consent form*: Blood draw volumes
- Item 22 Clarified in Appendix A, *Sample informed consent form*: Early termination
- Item 23 Added in Appendix B, *Approved birth control methods for transgender men (for sample informed consent form)*: Condom use and pregnancy testing
- Item 24 Corrected in Appendix D, *Tables of procedures (for sample informed consent form)*: Procedure timepoints

- Item 25 Updated in Appendices F through I: Assay locations, HVTN laboratory listings, and blood draw totals
- Item 26 Revised in Appendices G, H, K, and L: Table format and Schedule 3 blood draws at Visit #.X
- Item 27 Removed in Appendices G and H: Footnote regarding whole blood for HIV diagnostics
- Item 28 Clarified in Appendices J and M: Provision of HIV test results
- Item 29 Added as Appendix N: Protocol signature page
- Item 30 Revised in Letter of Amendment 1 to Version 2.0: Interim safety and feasibility assessments
- Item 31 Corrected: Minor typographical, grammatical, and formatting errors

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