FINAL

January 19, 2022

Clarification memo 1

Protocol

Version 2.0

HVTN 804/HPTN 095

Antiretroviral analytical treatment interruption (ATI) to assess immunologic and virologic responses in participants who received VRC01 or placebo and became HIV-infected during HVTN 704/HPTN 085

DAIDS-ES ID 38632

NON-IND PROTOCOL

HIV Vaccine Trials Network (HVTN) and HIV Prevention Trials Network (HPTN)
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

The changes described herein will be incorporated in the next version of Protocol HVTN 804/HPTN 095 if it undergoes full protocol amendment at a later time. New text is denoted in **bold underline**, deleted text in ~~strikethrough.~~

Item 1 Corrected in Appendix E, *Laboratory Procedures—Schedule 1: Monitoring ATI,* footnote 9

Footnote 9 in Appendix E, Laboratory Procedures- Schedule 1: Monitoring ATI, has been revised to correct an error. The number of days available for ATI Qualification Procedure prior to visit 4, was corrected from ~~14~~ to **28**, to harmonize with Appendix K: *Visit Windows*.

Footnote 9:

> [9]The ATI Qualification visit specimens must be obtained at least 28 days after ART switch. If needed, VL retesting may continue until viral suppression has been achieved (up to 84 days after ART switch). The last ATI qualification procedures must take place no more than ~~14~~**28** days prior to visit 4 (see HVTN 804/ HPTN 095 SSP for more information).

The Laboratory Procedures Table with the revised footnote is appended below.

Appendix E Laboratory procedures—Schedule 1: Monitoring ATI

Procedure	Ship to[1]	Assay location[1,2]	Tube Type[3]	Tube size (vol. capacity)[3]	Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
					Days on ATI:	D0	D7	D14	D21	D28	D35	D42	D49	D56	D70	D84	D98	D112	D126	D140	D154				
					Weeks on ATI:	W0	W1	W2	W3	W4	W5	W6	W7	W8	W10	W12	W14	W16	W18	W20	W22				
						Screening visit[15]	ART Switch[8]	ATI qualification[9]	ATI																
BLOOD COLLECTION																									
Screening or diagnostic assays																									
HIV PCR viral load[13]	Local labs	Local labs	EDTA	6mL		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
CD4+/CD8+ T-cell count[14]	Local labs	Local labs	EDTA	4mL		4	4	4	4	—	4	—	4	—	4	—	4	—	4	—	4	—	4	—	4	—
HBsAg/anti-HCV[4]	Local labs	Local labs	SST	5mL		10	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
QuantiFERON TB testing[5]	Local labs	Local labs	QFT Gold/Gold-Plus	1mL		4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Safety labs																									
Hgb / ANC / PLT	Local labs	Local labs	EDTA	4mL		4	4	4	4	—	—	—	4	—	—	—	4	—	4	—	4	—	4	—	4	—
ALT / direct bilirubin / eGFR	Local labs	Local labs	SST	5mL		5	5	5	5	—	—	—	5	—	—	—	5	—	5	—	5	—	5	—	5	—
Syphilis[10]	Local labs	Local labs	SST	5mL		5	—	—	5	—	—	—	5	—	—	—	5	—	5	—	5	—	5	—	5	—
Drug levels																									
ARV detection	CSR	TBD	EDTA	4mL		—	—	—	—	—	—	—	4	—	—	—	4	—	4	—	4	—	4	—	4	—
Immunogenicity & Virologic Assays																									
Cellular assays																									
ICS	CSR	HVTN labs	ACD	8.5mL		—	—	—	42.5	—	—	—	42.5	—	—	—	42.5	—	42.5	—	42.5	—	42.5	—	42.5	—
Phenotyping	CSR	HVTN labs	ACD	8.5mL		—	—	—	z	—	—	—	z	—	—	—	z	—	z	—	z	—	z	—	z	—
Humoral assays																									
Neutralizing antibody	CSR	HVTN labs	SST	8.5mL		—	—	—	8.5	—	—	—	8.5	—	—	—	8.5	—	8.5	—	8.5	—	8.5	—	8.5	—
FcR-mediated effector functions[6]	CSR	HVTN labs	SST	8.5mL		—	—	—	y	—	—	—	y	—	—	—	y	—	y	—	y	—	y	—	y	—
HIV reservoir assays	CSR	TBD	ACD	8.5mL		—	—	—	51	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Storage																									
Serum	CSR		SST	8.5mL		—	—	—	8.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Plasma	CSR		EDTA	10mL		—	—	—	—	—	—	—	—	—	—	—	10	—	10	—	10	—	10	—	10	—
PBMC	CSR		ACD	8.5mL		—	—	—	—	—	—	—	—	—	—	—	17	—	17	—	17	—	17	—	17	—
Visit total						38	19	19	134.5	6	10	6	79	6	10	6	106	6	106	6	106	6	106	6		
56-Day total						38	57	76	210.5	216.5	226.5	232.5	311.5	317.5	327.5	333.5	401.5	229	319	240	330	230	330	230		
URINE COLLECTION																									
Pregnancy Test[16]	Local labs	Local labs				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chlamydia/gonorrhea[7,10]	Local labs	Local labs				X	—	—	X	—	—	—	X	—	—	—	X	—	X	—	X	—	X	—	X	—
RECTAL SWAB COLLECTION																									
Chlamydia/gonorrhea[7,10]	Local labs	Local labs				X	—	—	X	—	—	—	X	—	—	—	X	—	X	—	X	—	X	—	X	—
OROPHARYNGEAL SWAB COLLECTION																									
Chlamydia/gonorrhea[7,10]	Local labs	Local labs				X	—	—	X	—	—	—	X	—	—	—	X	—	X	—	X	—	X	—	X	—
OTHER SPECIMEN COLLECTION																									
SARS-CoV-2 testing	Local labs	Local labs													X[18]										

[2] HVTN Laboratories include: Fred Hutchinson Cancer Research Center (Seattle, Washington, USA); Duke University Medical Center (Durham, North Carolina, USA). Non-HVTN laboratories: TBD.

[3] Local labs may assign appropriate alternative tube types for locally performed tests.

[4] HCV RNA PCR testing will be performed as a reflex test if indicated by anti-HCV antibody results.

[5] Tuberculin skin test (TST) will be performed if QuantiFERON TB testing is not available. See Procedures at CRS (Appendix H).

[6] FcR-mediated effector function assays may include ADCC, virion capture, and phagocytosis assays.

[7] Chlamydia/gonorrhea testing will be done on urine, and rectal and oropharyngeal swabs.

[8] The "ART switch" phase will only be performed for participants on NNRTIs. These participants will be considered enrolled on the first day of the new ART medication.

[9] The ATI Qualification visit specimens must be obtained at least 28 days after ART switch. If needed, VL retesting may continue until viral suppression has been achieved (up to 84 days after ART switch). The last ATI qualification procedures must take place no more than 28 days prior to visit 4 (see HVTN 804/HPTN 095 SSP for more information).

[10] In addition to STI testing at the marked visits, STI testing may occur at any visit if clinically indicated.

[11] Extended follow-up visit type A will occur every 6 months starting with 3 months after visit 27 continuing up to 3 years of this schedule. This follow-up visit may be performed for participants who have not met criteria to transition to Schedule 2 or Schedule 3 (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).

[12] Extended follow-up visit type B will occur every 6 months starting with 6 months after visit 27 continuing up to 3 years of this schedule, and then every 3 months thereafter. This follow-up visit may be performed for participants who have not met criteria to transition to Schedule 2 or Schedule 3 (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).

[13] A confirmatory sample should be drawn at the next visit (within approximately 1-2 weeks) following the first VL result ≥ 200 copies/mL (see Protocol Section 3.3.1 for details.

[14] A confirmatory sample should be drawn at the next visit (within approximately 1-2 weeks) following the first CD4+ T-cell count < 350 cells/mm^3 (see Protocol Section 3.3.2 for details.

[15] Screening visit specimens for participants not undergoing an NNRTI switch should be obtained no later than 2 weeks before Visit 4; see HVTN 804/HPTN 095 for more information.

[16] For persons capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

[17] At an early termination visit for a withdrawn or terminated participant (see Protocol Section 6.5), blood should be drawn as shown for Extended follow-up visit type A (see HVTN 804/HPTN 095 SSP for more information).

[18] SARS-CoV-2 testing may be performed at the screening visit and at any other visit, if clinically indicated. Testing must be by direct detection of SARS-CoV-2 (eg, nucleic acid or antigen detection). See HVTN 804/HPTN 095 SSP for more information.

y = SST blood collected for neutralizing antibody will also cover specimen needs for FcR-mediated effector functions; no separate blood draw is needed.

z = PBMC blood collected for ICS will also cover specimen needs for phenotyping; no separate blood draw is needed.

Protocol modification history

Protocol modifications are made via clarification memos, letters of amendment, or full protocol amendments. The version history of, and modifications to, Protocol HVTN 804/HPTN 095 are described below.

Date: January 19, 2022

Protocol version: Version 2.0
Protocol modification: Clarification memo 1

Item 1 Corrected in Appendix E, *Laboratory Procedures—Schedule 1: Monitoring ATI,* footnote 9

Date: August 27, 2021

Protocol version: 2.0
Protocol modification: Letter of Amendment 01

Item 1 Added in Section 5.2, *Exclusion criteria*, Section 6.1.1, *Screening*, Section 6.1.3, *ART switch*, Section 6.1.4, *ATI*, Section 6.2, *Schedule 2: Monitoring ATI with viremia*, Section 6.3, *Schedule 3: Follow-up on ART*, Section 10.1.1, *Risks of ATI*, Section 14, *Acronyms and abbreviations*, Appendix A: *Sample informed consent form*, and Appendices D through J: monitoring for SARS-CoV-2 infection during the study

Item 2 Updated in Section 2.10, *The necessity of the AMP placebo control group* and Appendix A, *Sample Informed Consent Form*: AMP participants have been unblinded

Item 3 Deleted in Appendices D, H and I: non-relevant footnotes

Item 4 Corrected in Section 6.1, *Schedule 1: Monitoring ATI*, and Section 6.3, *Schedule 3: Follow-up on ART*: cross reference to contraception status section Updated in Sections 5.3 and 16: Document reference

Item 5 Corrected in Appendix J, *Procedures at CRS—Schedule 3: Follow-up on ART*: placement of footnote 4 to visit 92 column

Item 6 Updated in Section 1.3, *Protocol Team*: protocol leadership members

Date: March 16, 2020

Protocol version: 2.0
Protocol modification: Full Protocol Amendment 1

Item 1 Clarified in Section 1, *Protocol summary*: Study population description

Item 2 Revised in Sections 3.3.1 through 3.3.3 and in footnotes to Appendices E and F: Timing for viral load and CD4 count confirmatory testing

Item 3 Revised in Sections 5.1, *Inclusion criteria* and 5.2, *Exclusion criteria*: VL assay qualification

Item 4 Updated in Sections 5.3 and 16: Document reference

Item 5 Clarified in Section 6.5 and footnote to Appendix J: Procedures at early termination visit

Item 6 Clarified in Section 11.1.1: PSRT meeting frequency

Item 7 Added in Section 11.2.3, *AE reporting*: Exception for eGFR reporting

Item 8 Removed in Section 13, *Protocol conduct*: Reference to randomization

Item 9 Updated in Section 15: Protocol version history

Item 10 Corrected and clarified in Appendix A, *Sample informed consent form*: Study objectives, ATI duration, ATI qualification visit, follow-up for those who decline ART restart, data provision to participants, follow-up till viral resuppression, lab locations, and potential other studies

Item 11 Corrected in Appendix C, *Sample consent form for use of samples and information in other studies*: Section 13 checkbox text

Item 12 Corrected in Appendix D: Table of procedures for Part 2

Item 13 Added to HVTN Laboratories in Appendices E, F, and G: Fred Hutchinson Cancer Research Center (Seattle, Washington, USA)

Item 14 Corrected in Appendix G, *Laboratory procedures—Schedule 3: Follow-up on ART*: CT/GC testing by urine at Visits 87, 88, and 90

Item 15 Corrected in Appendix H footnotes: Visit number reference and typographical error

Item 16 Corrected: Typographical and copy-editing errors

Item 17 Corrected in Section 3.3.4: Visit schedule references

Item 18 Corrected in Section 5: Study population description

Date: November 13, 2019

Protocol version: 1.0
Protocol modification: Original protocol