FINAL

March 22, 2022

Full protocol amendment 2

A summary of changes to:

Protocol

Version 3.0

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

Title of study

DAIDS-ES ID 38632

NON-IND Protocol

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

The following information impacts the HVTN 804 / HPTN 095 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 RE approval(s) for this amendment, CRSs must implement the amendment immediately.

Upon receiving final IRB/EC and any other applicable RE approval(s), CRSs are required to submit amendment registration documents to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). CRSs will receive an Amendment Registration Notification 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 Amendment Registration Notification, along with this amendment and any IRB/EC and RE correspondence, should be retained in the CRS'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. The CRS's IRB/EC is responsible for determining the process of informing study participants of the contents of this full protocol amendment.

List of changes

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

In view of the COVID-19 pandemic, we have included language throughout the protocol that aims to mitigate the risk of a SARS-CoV-2 infection for participants who will be screened and enrolled in the ATI study. The specific changes to the protocol are itemized below.

A Section 5.2, *Exclusion Criteria*: Two new criteria were added (new #10 and #13)

Added a new criterion #10 excluding volunteers who have received any emergency-use authorized, WHO emergency use listed, licensed or registered SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) vaccine within 4 weeks before planned ART interruption.

Added a new criterion #13 specifying that COVID-19 symptomatic or asymptomatic volunteers who test positive for SARS-CoV-2 test (direct viral detection, eg, viral nucleic acid or antigen detection) ≤ 14 days of enrollment are now excluded from the study. However, volunteers who have residual symptoms consistent with resolved COVID-19 (e.g., persistent loss of taste, persistent cough) may be enrolled based on the clinical judgement of the investigator.

Subsequent criterion numbers have been revised.

B Section 6.1.1, *Screening*: SARS-CoV-2 testing and SARS-CoV-2 risk reduction counselling

In paragraph 2: added a new bullet point #6, which specifies that SARS-CoV-2 risk reduction counselling will be offered to volunteers at the discretion of the clinician, based on local epidemiology. Also added a new bullet point #10, which specifies that volunteers who have not received any COVID-19 vaccine will be tested for SARS-COV-2.

C Section 6.1.3, *ART Switch*: SARS-CoV-2 testing and SARS-CoV-2 risk reduction counselling

In sub-sections *ART Switch,* paragraph 2: added a new bullet point #5, which specifies that SRAS-CoV-2 risk reduction counselling will be offered to volunteers at the discretion of the clinician, based on local epidemiology. Also added a new bullet point #10, which specifies that volunteers who have not received any COVID-19 vaccine will be we be tested for SARS-COV-2, per clinician judgement based on local epidemiology and/or symptom presentation.

The same specifications were added in sub-section *ATI qualification visit*, paragraph 1, bullet points #5 and #8

D Section 6.1.4, *ATI*: SARS-CoV-2 testing and SARS-CoV-2 risk reduction counselling

In paragraph 2: added a new bullet point #6, which specifies that SRAS-CoV-2 risk reduction counselling will be offered to volunteers at the discretion of the clinician, based on local epidemiology. Also added a new bullet point #13, which specifies that volunteers who have not received any COVID-19 vaccine will be we be tested for SARS-COV-2 as per the clinician's judgement based on local epidemiology and/or symptom presentation.

E Section 6.2, *Monitoring ATI with viremia*: SARS-CoV-2 testing and SARS-CoV-2 risk reduction counselling

In paragraph 1: added a new bullet point #6, which specifies that SRAS-CoV-2 risk reduction counselling will be offered to volunteers at the discretion of the clinician, based on local epidemiology. Also added a new bullet point #13, which specifies that volunteers who have not received any COVID-19 vaccine will be we be tested for SARS-CoV-2 as per the clinician's judgement based on local epidemiology and/or symptom presentation.

F Section 6.3, *Schedule 3: Follow-up on ART*: SARS-CoV-2 testing and SARS-CoV-2 risk reduction counselling

In paragraph 1: added a new bullet point #5, which specifies that SRAS-CoV-2 risk reduction counselling will be offered to volunteers at the discretion of the clinician, based on local epidemiology. Also added a new bullet point #12, which specifies that volunteers who have not received any COVID-19 vaccine will be tested for SARS-COV-2 as per the clinician's judgement based on local epidemiology and/or symptom presentation.

G Section 10.1.1, *Risks of ATI:* risk of COVID-19

The impact of contracting a SARS-CoV-2 infection and COVID-19 has not yet been well studied in people living with HIV, much less in people undergoing an ATI. Paragraph 1 in this section has been updated with risk language to reflect this.

H Section 14, *Acronyms and abbreviations:* spelled out SARS-CoV-2

I Appendix A, *Sample informed consent form*, Key information and in Risks*:* risk of COVID-19

As mentioned in sub-Item G of this amendment, risk language regarding SARS-CoV-2 and COVID-19 during an ATI has been added to Section 10.1.1. In order to harmonize this with the SICF, we have updated sub-Section Key information,

paragraph 1 (added new bullet point #9) and in sub-Section Risks, heading 19, *There are risks to being in this study*.

J Appendix A, *Sample informed consent form,* Joining the study and in Being in the study: SARS-CoV-2 testing and SARS-CoV-2 risk reduction counselling

As previously mentioned in sub-Items B, C, D, E and F of this amendment, volunteers will be tested for SARS-CoV-2 and risk reduction counselling will be offered as needed. Language to reflect this is included in:

- Joining the study: sub-Section 4, *If you want to join the study, we will screen you to see if you are eligible*, paragraph 2.

- Being in the study: sub-Section 8*, If you join the study, we will collect some basic information.*

K Appendix D, *Tables of procedures for sample informed consent form*: SARS-CoV-2 testing and SARS-CoV-2 risk reduction counselling

New study procedures to enable SARS-CoV-2 testing and risk reduction counseling at screening or any study visit as needed, have been added to all the tables in Appendix D indicating that it will be performed "at screening or any study visit as needed". This was done to harmonize Appendix D with the revised Sections 6.1.1, 6.1.3, 6.1.4, 6.2 and 6.3.

L Appendix E, *Laboratory procedures — Schedule 1*: Monitoring ATI; Appendix F, *Laboratory procedures — Schedule 2*: Monitoring ATI with viremia; Appendix G, *Laboratory procedures — Schedule 3*: Follow-up on ART: Specimen collection for SARS-CoV-2 testing

A new procedure has been added to all the tables in the appendices mentioned above, to enable specimen collection for SARS-CoV-2 testing. A new associated footnote has been added to the footnote list for each table to specify that testing will be done, if clinically indicated. Subsequent footnotes have been renumbered accordingly. The tables have been updated to harmonize laboratory procedures with the revised Sections 6.1.1, 6.1.3, 6.1.4, 6.2 and 6.3.

M Appendix H, *Procedures at CRS — Schedule 1*: Monitoring ATI; Appendix I, *Procedures at CRS — Schedule 2*: Monitoring ATI with viremia; Appendix J, *Procedures at CRS — Schedule 3*: Follow-up on ART: SARS-CoV-2 risk reduction counselling

"SARS-CoV-2 risk reduction counseling" with checkmarks at all visits has been added as a study procedure to all the tables in Appendices H, I and J. A new associated footnote has been added to the footnote list for each table to specify that SARS-CoV-2 risk reduction counseling will be provided at any visit, if indicated.

Subsequent footnotes have been renumbered accordingly. The tables have been updated to harmonize procedures at CRS with the revised Sections 6.1.1, 6.1.3, 6.1.4, 6.2 and 6.3.

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

The AMP study is unblinded and participants are being informed if they received the study antibody or a placebo. The last sentence of paragraph 10 has been updated in Section 2.10 to reflect this information. In Appendix A, paragraph 3 had been updated to harmonize with the revised Section 2.10.

Item 3 Deleted in Appendix D, *Tables of procedures for sample informed consent form;* Appendix H, *Procedures at CRS—Schedule 1: Monitoring ATI* and in Appendix I, *Procedures at CRS—Schedule 2: Monitoring ATI with Viremia:* deleted non-relevant footnotes

Appendices D, H, and I have multiple tables within one appendix. Some footnotes are not relevant to all the tables within the given appendix. We have corrected this by deleting non-relevant footnotes from the footnote list. The specific changes are listed below:

- In Appendix D, **footnote d** has been deleted from the footnote list in the first table titled "Table of procedures for Part 1: Screening and stopping your HIV medications". **Footnote c** has been deleted from the footnote list in the table titled "Table of procedures for Part 2: Monitoring your health and your HIV".

- In Appendix H, the **last 3 footnotes, numbered 8, 9, and 10**, have been deleted from the footnote list in first table of the Appendix.

- In Appendix I, the last 3 footnotes, numbered 4, 5 and 6, have been deleted from the footnote list in first table of the Appendix.

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

In Section 6.1, the cross reference to contraception status assessment was mentioned as Section 6.5 instead of Section 6.6. We have corrected this throughout Section 6.1, specifically: Section 6.1.1 (7^{th} bullet), Section 6.1.3 (6^{th} bullet) and Section 6.1.4 (7^{th} bullet). We have also corrected the error in cross reference in Section 6.3 (6^{th} bullet) and revised the reference from Section 6.4 to Section 6.6.

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

Footnote 5 notes that visit 92 procedures will be followed if there is early termination visit for a withdrawn or terminated participant. Therefore, the placement of this footnote has been moved from visit 91 column to visit 92 column.

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

There has been a change in the Medical Officers overseeing this study. The Protocol Leadership table has been updated to reflect this change.

Item 7 Corrected in Appendix E, *Laboratory Procedures—Schedule 1: Monitoring ATI:* corrected 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*.

Item 8 Updated Section 15, *Version History*: Modifications to version 2.0 and contents of this amendment.

Section 15 was updated to add the following: Letter of Amendment 1, dated August 27, 2021 for version 2.0; Clarification Memo 1, dated January 19, 2022 for version 2.0 and Full Protocol Amendment 2, dated March 7, 2022.

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: March 22, 2022

Protocol version: Version 3.0
Protocol modification: Full protocol amendment 2 (to incorporate changes from LoA1 and CM1 to the protocol version 2.0)

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 Appendix D, *Tables of procedures for sample informed consent form;* Appendix H, *Procedures at CRS—Schedule 1: Monitoring ATI* and in Appendix I, *Procedures at CRS—Schedule 2: Monitoring ATI with Viremia:* deleted 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

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

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

Item 7 Corrected in Appendix E, *Laboratory Procedures—Schedule 1: Monitoring ATI:* corrected footnote 9

Item 8 Updated Section 15, *Version History*: Modifications to version 2.0 and contents of this amendment.

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