

**SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:**

HPTN 052

**A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV
Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In
Serodiscordant Couples
Version 2.0 / 24 May 2004**

**THE AMENDED PROTOCOL IS IDENTIFIED AS:
Version 3.0 / 20 November 2006**

IND # 68,535

Information/Instructions to Study Sites from the Division of AIDS

Prior to implementing the changes in this amendment, HPTN 052 study sites will submit this Summary of Changes, Version 3.0 of the protocol, and the revised site-specific informed consent forms to all relevant regulatory authorities and Institutional Review Boards and/or Ethics Committees (IRBs/ECs). Both IRB/EC approval and completion of the protocol registration process are required before implementing the modifications contained in this amendment.

Issuance of this amendment requires preparation of revised study informed consent forms for the study. These forms must be labeled with protocol Version 3.0 and must be used when obtaining informed consent for screening, enrollment, specimen storage, and pregnancy after obtaining IRB/EC approval of the amendment and completing protocol registration procedures with the DAIDS Protocol Registration Office. All previously enrolled study participants will be re-consented with the revised informed consents forms.

Please file this Summary of Changes, Version 3.0 of the protocol, corresponding site-specific informed consent forms, and all associated IRB/EC correspondence in your essential document files for HPTN 052.

The Division of AIDS Regulatory Affairs Branch will submit this amendment to the United States Food and Drug Administration for inclusion in Investigational New Drug (IND) application #68,535.

RATIONALE

A run-in period phase of HTPN 052 was conducted under Version 2.0 of the protocol. The purpose of the run-in period was to determine the feasibility of conducting the study, and to make appropriate adjustments to the protocol based on this experience prior to implementation of the full study. Some of the revisions made in Version 3.0 reflect information learned from the run-in period. In addition, upon review by the NIAID DSMB, it was determined that the CD4+ cell count used for ART initiation in Arm 2 (delayed arm) required modification in accordance with current WHO guidelines. Finally, to the extent possible, and as requested by the sponsor (DAIDS), the protocol has been aligned with ACTG A5175 with regard to the management of ART and HBV-HIV co-infection, as well as the inclusion and exclusion criteria, so that data from both studies may be compared.

SUMMARY OF MAJOR REVISIONS AND JUSTIFICATION

This amendment incorporates two previously approved protocol Letters of Amendment as well as the following significant protocol modifications:

- Information specific to the run-in period has been removed as that phase of the study has been completed. Version 3.0 of the protocol focuses on implementation of the full study.
 - Arm 2 (the delay arm) has been modified to initiate ART at a CD4+ cell count within or below the range of 200-250 cells/mm³ as recommended by the NIAID DSMB and in accordance with the current WHO guidelines for the initiation of ART.
 - Information for Kaletra[®]/Aluvia[®] and Truvada[®] has been added as these drugs are now provided for the study.
 - The protocol now allows the use of ART that is not provided by the study after prior consultation with the HPTN 052 CMC. This is in anticipation of the need for additional drugs to manage secondary and salvage therapy, as well as in recognition of the fact that additional drugs may become available over the course of the study.
 - The protocol has been revised to allow resistance testing where available, and indicates that it may be used to guide selection of secondary regimens. This change reflects the changing technology and capabilities at the participating sites.
 - Viral load testing has been added at 4 weeks after ART initiation and quarterly thereafter. This additional testing allows for closer monitoring of viral load after ART initiation.
 - The collection of stool and urine samples for parasitic testing, as well as malaria testing, have been removed from the protocol. These data were deemed non-critical to the study objectives and endpoints. Investigators may test for these conditions at any time if clinically indicated.
 - As requested by DAIDS, the ART management sections of the protocol, as well as specific guidelines for the management of HBV-HIV co-infection, have been revised to closely align with the information in ACTG A5175.
 - The inclusion and exclusion criteria have been revised because of the modification of Arm 2 (the delay arm) and to align the protocol with ACTG 5175.
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SUMMARY OF CHANGES

General Updates

- Updated title page, list of protocol co-chairs, table of contents, team roster, acronyms, schema, and references.
- Merck & Co., Inc. has been added as providing pharmaceutical support to the study.
- Renumbered sections and tables as required.
- Minor editorial and typographical updates and corrections have been made.

Section 1.0: Introduction

- Revisions were made to the study rationale to include new information regarding ART initiation as well as additional clinical research and guidelines addressing the expected benefit of ART on HIV transmission and prevention.
- Information was added for Truvada[®] and Kaletra[®]/Aluvia[®].
- The information for Combivir[®], zidovudine, lamivudine, efavirenz, nevirapine, tenofovir, and didanosine was revised.
- The subsection on the initiation of ART (Section 1.2.4.2) was revised to take into account current WHO guidelines.
- The subsection on HIV-1 drug resistance (Section 1.2.4.3) was revised to remove language prohibiting the use of local genotyping results for clinical management.
- Table 1 was revised to include new information on predominant subtypes.
- The subsection on additional substudies (Section 1.2.4.4) was revised to include information about CHAVI.
- The subsection describing the study's implementation plan (Section 1.3) was revised to remove unnecessary information about the run-in period as it has now been completed.

Section 2.0: Study Objectives and Study Design

- The primary objective of the study was revised to indicate that ART will be initiated in the delay arm when CD4+ cell counts fall between 200 and 250 cells/mm³.
- A secondary objective to characterize and compare quality-of-life (QOL) indicators in different geographic settings and by antiretroviral treatment strategies was added.
- The subsection describing the study design (Section 2.3) was revised to indicate the following:
 - Upon entry, Index cases must have a CD4+ cell count between 350 and 550 cells/mm³.
 - The duration of the full study will be 78 months.
 - Kaletra[®]/Aluvia[®] and Truvada[®] have been added to the protocol.
 - The use of study-provided and non-study-provided drugs in the primary, secondary, and salvage regimens.
- A subsection addressing the initiation of ART in the delay arm (Arm 2) was added (Section 2.3.1).
- The subsection containing the criteria for switching antiretroviral therapy due to virologic failure (Section 2.3.2) was revised to encourage repeat viral load testing within a month's timeframe, to allow local resistance testing to guide clinical management, and to mandate a switch to a secondary regimen if viral load remains greater than 1000 copies/mL for eight weeks or longer unless a longer delay is approved by the HPTN 052 CMC.
- Conducting sexual history assessments at Month 1 and Month 2 has been removed from the subsections on Index case and Partner follow-up (Sections 2.3.3.1 and 2.3.3.2).

Section 3.0: Study Population and Screening, Recruitment, and Enrollment Procedures

- The inclusion criteria for the Index case have been modified in the following ways:
 - The algorithm required to determine HIV positive serology has been added.
 - All inclusion criteria related to pregnancy, breastfeeding, and required contraception have been removed.
 - A note was added indicating that if a woman is in her first trimester during screening, the HTPN 052 CMC **must** be consulted prior to enrollment.
 - The range of CD4+ cell count allowed for study entrance has been changed from 300-500 cells/mm³ to 350-550 cells/mm³.
 - The allowable hemoglobin value has been changed from ≥ 7.0 g/dL to ≥ 7.5 g/dL.
 - Calculated creatinine clearance ≥ 60 mL/min has been added.
 - Absolute neutrophil count ≥ 750 mm³ or $0.750 \times 10^9/L$ has been added.
- The inclusion criteria for the Partner have been modified in the following way:
 - The algorithm required to determine HIV negative serology has been added.
- The exclusion criteria for the Index case have been modified in the following ways:
 - Pregnancy has been removed as an exclusion criteria.
 - Documented or suspected acute hepatitis within 30 days prior to enrollment, irrespective of AST or ALT is a study exclusion regardless of what regimen the participant begins at enrollment.
 - Acute therapy for serious medical illnesses within 14 days prior to enrollment has been added.
 - Radiation therapy or systemic chemotherapy within 45 days prior to enrollment has been added.
 - Any immunomodulator or other investigational therapy within 30 days prior to enrollment has been added.
 - Active drug or alcohol use or dependence that would interfere with study participation has been added.
 - Vomiting or inability to swallow medications due to an active, pre-existing condition that prevents adequate swallowing and absorption of study medication has been added.
 - Need for a prohibited medication as defined in the protocol has been added.
 - Allergy or sensitivity to any study drugs or their formulation has been added.
- The exclusion criteria for both the Index case and Partner have been modified in the following way:
 - “Previous and/or current participation in an HIV vaccine study” has replaced “the receipt of an experimental HIV vaccine” as the exclusion criteria.

Section 4.0: Study Treatment Considerations

- Truvada[®] and Kaletra[®]/Aluvia[®] have been added to the list of drugs being provided by the study.
- This section was revised to clarify the following points:
 - Combivir[®] and efavirenz or atazanavir are recommended as the primary regimen.
 - Study clinicians may use other study-provided ART in the starting regimen after obtaining permission from the HPTN 052 CMC.
 - Secondary and salvage regimens are not defined by the protocol and may contain any viable combination of three or more of the HPTN 052-provided study drugs.
 - Non-study-provided ART may be used in secondary and salvage regimens if approved by the HPTN 052 CMC.

- Tables 3, 4a, 4b, 5, 6, and 7 were revised to align with the information in ACTG A5175 as well as to add information for Truvada[®] and Kaletra[®]/Aluvia[®], where appropriate.
- The subsection on precautionary medications (Section 4.3.3) was revised to align with the information in ACTG A5175.
- The subsection on adherence counseling and assessment (Section 4.4) was revised to indicate the tools being used to measure adherence.
- The subsection on toxicity management (Section 4.5) was revised to align with the information in ACTG A5175.
- A subsection on the management of HBV-HIV co-infection (Section 4.6) was added.

Section 5.0: Study Procedures, Clinical Procedures, and Laboratory Evaluations

- The following changes were made to the screening visit (Section 5.1):
 - Demographic information is no longer being collected.
 - Use of the eligibility checklist is no longer a protocol requirement.
 - Testing for hepatitis B has been added.
 - Plasma and serum samples are no longer being collected for long-term storage.
- The following changes were made to the enrollment visit (Section 5.2):
 - Demographic information is being collected.
 - A quality-of-life assessment is being performed for Index cases.
 - Stool and urine samples are no longer being collected for parasitic disease testing.
 - Malaria testing is no longer being done.
 - Hepatitis B testing is no longer being done.
 - PBMCs will be collected on all participants, not just a subset.
- Information was added reminding study staff that additional assessments/procedures may be required based on the ART-related sections of the protocol (Section 5.3).
- Information was added to clearly indicate when the week two visit should take place (Section 5.3.1).
- The following changes were made to the monthly visits (Section 5.3.2):
 - The sexual history assessment is no longer done at Month 1 and 2.
 - A note was added to remind staff **not** to collect a blood sample unless the visit is one of the first two monthly visits following ART initiation.
 - Viral load testing was added one month after ART initiation.
- The following change was made to the quarterly visits (Section 5.3.3):
 - A quality-of-life assessment is being performed for Index cases.
 - PBMCs will be collected on all participants, not just a subset.
- The following changes were made to the annual visits (Section 5.3.4):
 - A quality-of-life assessment is being performed for Index cases.
 - Stool and urine samples are no longer being collected for parasitic disease testing.
 - Malaria testing is no longer being done.
 - TB testing (PPD/chest x-ray) is no longer a requirement for the U.S. site.
 - PBMCs will be collected on all participants, not just a subset.
- Criteria for permanent treatment discontinuation (off treatment/on study) were added (Section 5.3.5).
- The following change was made to the partner seroconversion visit (Section 5.3.6):
 - PBMCs will be collected on all participants, not just a subset.
- Procedures for an ART initiation visit were added (Section 5.3.7).

- The following change was made to the visit associated with virologic failure (Section 5.3.8):
 - Information was added to clearly indicate the procedures that should take place after virologic failure, and that these procedures should not be done until virologic failure has been confirmed.
 - A note was added indicating that the results from the viral load testing performed for confirmation of virologic failure may be used as the value reported for this visit.
- Instructions for how to report pregnancies to the ART Pregnancy Registry were included (Section 5.4).
- Safety and ART regimen information was added to the subsections covering pregnancy and breastfeeding (Section 5.4).
- Information has been included for women with reproductive potential and the management of contraception and ART (Section 5.5).
- Information has been added addressing the use of nPEP in this study (Section 5.6).

Section 6.0: Adverse Event (AE) and Expedited Adverse Event (EAE) Reporting

- The current versions of the DAIDS EAE manual and grading table are referred to in the text.
- Clarifies that, in general, EAEs will not be reported for Index cases not on ART or for Partners; however, if an event occurs that fits the regulatory definition of an SAE and can be associated with study participation or procedures, it will be reported as an EAE.
- Table 8 was added as a reference guide for reporting AEs and EAEs.

Section 7.0: Statistical Considerations

- This section was revised to indicate that the run-in period has been completed.
- Table 9 in Section 7.2.2 and the text in Section 7.6.2 were revised to include analysis of the quality-of-life assessment.
- Revisions were made to include the change in CD4+ cell count used for inclusion criteria and ART initiation.
- Information was added to the subsection on monitoring the quality of study conduct (Section 7.7.1) to indicate how recruitment targets and HIV acquisition rates will be assessed and at what point the study will be stopped or modified.
- A definition of futility was added to Section 7.7.2.

Section 8.0: Human Subjects Considerations

- Information about certain aspects of ethical review was removed as these details are contained in the HPTN MOP.
- The requirement that all study records containing names or other personal identifiers be stored separately from other study records has been removed.

Section 9.0: Laboratory Specimens and Biohazard Containment

- Malaria testing and the collection of stool and urine samples for the diagnosis of parasitic diseases have been removed.
- The requirement of compliance with IATA shipping regulations has been added.

Section 10.0: Administrative Procedures

- The information stating that the DAIDS SOPs, EAE manual, and toxicity grading table can be found in the SSP has been removed as it is inaccurate.
- Detailed information about the coordination between the protocol team members has been removed.

Appendix IA and IB

- The Schedules of Procedures and Evaluations for both the Index case and the Partner were revised to reflect the changes made to the protocol.

Appendix III

- Appendix III and IV from Version 2.0 were combined and revised to create one list of AIDS-defining illnesses to be used for eligibility determination and as part of the criteria to initiate ART in the delay arm.

Appendix IV

- The following informed consent forms (ICFs) were removed as the run-in period has been completed and they are no longer relevant.
 - Index case and Partner screening: run-in period and full study
 - Index case enrollment: run-in period and full study
 - Partner enrollment: run-in period and full study
- The remaining ICFs (screening, enrollment Index case, enrollment Partner, stored specimens, and pregnancy) were revised to reflect the changes made to the protocol.

Appendix VI

- In Version 2.0 of the protocol, Appendix VI contained the DAIDS EAE Reporting Manual. This has been removed from the protocol as it is now available on the DAIDS Regulatory Compliance Center website.