

Letter of Amendment # 1 to:

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 3.0, November 20, 2006, DAIDS Document ID: 10068

Final Version: 7 August 2007

The following information impacts the HPTN 052 study and must be forwarded to all responsible Institutional Review Boards (IRBs)/Ethics Committees (ECs) as soon as possible for their information and review. This Letter of Amendment must be approved by all responsible IRBs/ECs before implementation.

The modifications in this Letter of Amendment do not result in any changes to the informed consent forms. Therefore, subjects who previously provided informed consent and are enrolled in the study need not be re-consented unless otherwise specified by the IRB(s)/EC(s).

This Letter of Amendment and any IRB/EC correspondence must be filed in the site regulatory file and in other pertinent files. Submission of these documents to the DAIDS/RCC Protocol Registration Office is NOT required unless the changes result in a change to the informed consent form for the site.

If the HPTN 052 protocol is amended in the future, this Letter of Amendment will be incorporated into the next version.

Summary of Revisions and Rationale

- 1a-l. The protocol roster has been revised to delete Sanjay Mehendale, Paul Kaufman, Benoit Masse, Carolyn Yanavich, Rozina Khanna, and Edde Loeliger as they are no longer protocol team members. Sheela Godbole, Diane Havlir, Heather Ribaldo, Christina Lalama, Susan Swindells, and Ian Sanne have been added as new protocol team members.
- 2a-b. One of the secondary objectives in the schema and in Section 2.2 has been revised to include HIV-related illnesses and other targeted medical conditions. Information regarding these additional conditions will be used to compare outcomes and survival by geographic location and antiretroviral treatment strategy.
3. Section 4.5.5.11 has been revised to reflect that hypophosphatemia should be monitored “for participants on TDF only”. The package insert for Viread (TDF) indicates that “renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association the use of VIREAD” [TDF]. Thus, hypophosphatemia will only be monitored closely when participants are on TDF. Such close monitoring of hypophosphatemia is not necessary for the other drugs included in the protocol. This information was included in V. 2.0 of the HPTN 052 protocol, but was inadvertently left out of V. 3.0.
4. Section 5.4.4 has been revised to reflect that in pregnant women, triple regimen ART will not be required after the birth of the child, since in some settings women are encouraged not to breastfeed and therefore, should not be required to continue ART after the birth. At the discretion of the site clinician, ART may be continued after birth if the mother is breastfeeding.

Summary of Revisions and Rationale (continued)

- 5a-b. Section 7.2.2 (Table 9) and Section 7.6.2 have been revised to include the analysis for the additional HIV-related illnesses and other targeted medical conditions added to the secondary objectives (see 2a-b above).
- 6a-d. An additional appendix (Appendix IV) has been added that outlines all medical conditions that will be used for analysis of the revised secondary objective (see 2a-b above). Previous references to Appendix IV have been relabeled as Appendix V.
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Implementation of the Protocol Modification

The modifications detailed below will be formally incorporated into the body of the protocol with the next full amendment. Deletions to the protocol text are indicated by ~~striketrough~~; additions are indicated in **bold**.

Revision 1a Protocol Roster

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Revision 2a Schema (secondary objectives)

- Determine, characterize, and compare the rates of AIDS-defining **and HIV-related** illnesses, sexually transmitted diseases, opportunistic infections, ~~and~~ immune reconstitution syndromes, **and other targeted medical conditions**, with regard to outcomes and survival as observed in different geographic settings and by antiretroviral treatment strategies.

Revision 2b Section 2.2, Secondary Objectives

- Determine, characterize, and compare the rates of AIDS-defining **and HIV-related** illnesses, sexually transmitted diseases, opportunistic infections, ~~and~~ immune reconstitution syndromes, **and other targeted medical conditions**, with regard to outcomes and survival as observed in different geographic settings and by antiretroviral treatment strategies.

Revision 3 Section 4.5.5.11, Hypophosphatemia (**for participants on TDF only**)

Revision 4 Section 5.4.4 Procedures for Women Not on ART Who Become Pregnant

If an index case not on ART (Arm 2) becomes pregnant, she must sign a pregnancy informed consent form in order to continue her participation in the study. Once consent is obtained, she will be followed per the schedule of procedures and evaluations and will be placed on a triple regimen of ART appropriate for use during pregnancy regardless of CD4+ cell count at approximately the beginning of the 2nd trimester of pregnancy (*e.g.* 12-14 weeks of pregnancy); ~~and for 4-6 weeks following birth.~~ The ART will be provided through the study. The choice of regimen for such women should be documented in the study participant's chart and on any applicable CRFs. It should be noted that ddI-EC and d4T must not be coadministered. ATV may not be included in the regimen of any study participant who is pregnant.

Revision 5a Section 7.2.2, Secondary Endpoints (Table 9: Secondary Endpoints, the measurements for safety and toxicity of treatment)

- Time from enrollment to time of first development and any subsequent occurrence of Grade 3 or 4 ART-related toxicities
- ~~Time from enrollment to time of first serious AIDS-related events (Grade 4 and higher)~~
- Time from enrollment to time of first serious cardiovascular or other metabolic events (Grade 4 and higher)
- Time from enrollment to time of first Grade 4 and higher events (any event)
- **Time from enrollment to time of first occurrence of any HIV/AIDS-related event (see Appendix IV for qualifying events) or death**
- **Time from enrollment to time of first occurrence of any HIV/AIDS-related event or WHO disease Stage 2 or 3 (see Appendix IV for qualifying events)**
- **Time from enrollment to time of first occurrence of any other targeted medical condition (see Appendix IV for qualifying events)**
- **Time from enrollment to time of occurrence of any condition outlined in Appendix IV or death**

Revision 5b Section 7.6.2, Secondary Analysis

Many secondary analyses will be performed using the secondary endpoints described in Table 9. Time-to-event secondary endpoints will be analyzed according to the Kaplan-Meier method where treatment strategy differences will be tested using the stratified log-rank test while secondary endpoints involving repeated assessment over time (*e.g.*, adherence and sexual behavior) will be compared at selected time points. At each of the selected time points, comparison of the two treatment arms will be made using Fisher exact test or Wilcoxon rank-sum test as appropriate. More generally, GEE (Generalized Estimating Equation)⁷² methods and robust variance estimates will be used to evaluate treatment effect and trends over time. These analyses will be used to compare between the two arms outcomes related to mortality, disease progression, morbidity, safety, toxicity, and transmission of HIV drug resistant virus. A complete set of secondary endpoints to be analyzed is listed in Table 9. As for the primary analysis, the proportionality of the hazards over time will be evaluated using similar methods as describe in Section 7.6.1. **Treatment differences involving multivariate failure time data will be evaluated by the Andersen-Gill proportional hazards model based on counting processes with robust variance estimates.**

Revision 6a Table of Contents

APPENDIX IV – **Medical Conditions for Additional Data Collection**

APPENDIX IV – Sample Informed Consent Forms

Revision 6b Section 8.2, Informed Consent, first paragraph

Written informed consent will be obtained from each study participant (or a mark for those who are illiterate, which will be witnessed by a third party). Each study site is responsible for developing study informed consent forms for local use, based on the templates in Appendix IV, that describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations.

The following HIV/AIDS-related illnesses (WHO Stage 4, severe bacterial infections, and pulmonary TB), WHO Stage 2 and 3 clinical events, and other targeted medical conditions have been identified for secondary endpoint analysis. The occurrence of these conditions during the study may trigger the collection of additional information, which may be collected retrospectively, for inclusion in the study database according to the instructions in the Study-Specific Procedures (SSP) manual. The confirmed and probable definitions of these conditions can be found in the current ACTG Criteria for Clinical Events and Other Diseases <http://www.fstrf.org/ACTG/appendices/appendices.html>).

Note: WHO HIV/AIDS clinical staging based on the following reference: World Health Organization. WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children. 7 August 2006, pp. 15-16.

HIV/AIDS-related Illnesses (WHO Stage 4, severe bacterial infections, and pulmonary TB):

- Bacterial infections, severe (*e.g.*, pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
- Bacterial pneumonia, recurrent, severe (≥ 2 episodes in 12 months)
- Candidiasis of bronchi, trachea, lungs, oesophageal, or persistent oral
- Cervical carcinoma, invasive, confirmed by biopsy
- Chagas' disease
- Cryptococcosis, extrapulmonary including meningitis
- Cryptosporidiosis, chronic intestinal (> 1 month duration)
- Cytomegalovirus disease (retinitis or infection of other organs)
- Encephalopathy, HIV-related
- Herpes simplex, chronic (orolabial, genital, or anorectal site, > 1 month duration), or bronchitis, pneumonitis, esophagitis, or visceral at any site
- Isosporiasis, chronic intestinal (> 1 month duration) (confirmatory diagnostic testing required)
- Kaposi's sarcoma
- Leishmaniasis, atypical, disseminated
- Lymphoma, Burkitt, immunoblastic, primary central nervous system/cerebral, B-cell non Hodgkin (confirmatory diagnostic testing required)
- *Mycobacterium avium* complex (MAC) or *M. kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, (pulmonary or extrapulmonary)
- Mycobacterial infection, other species or unidentified species, disseminated or extrapulmonary
- Mycosis, disseminated (extrapulmonary histoplasmosis or coccidiomycosis)
- Penicilliosis, disseminated
- Pneumocystis pneumonia

- Progressive multifocal leukoencephalopathy (PML)
- Septicemia, recurrent, including non-typhoidal *Salmonella*
- Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy
- Toxoplasmosis of brain/central nervous system
- Wasting syndrome due to HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (>=2 loose stools per day >=1 month) or chronic weakness and documented fever >=1 month

WHO Stage 2 and 3 Clinical Events:

Stage 2

- Moderate, unexplained weight loss (<10% body weight)
- Upper respiratory tract infections, recurrent (sinusitis, tonsillitis, otitis media and pharyngitis)
- Herpes zoster
- Angular cheilitis
- Oral ulcerations, recurrent
- Papular puritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infections

Stage 3

- Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis
- Unexplained severe weight loss (>10% body weight)
- Unexplained chronic diarrhea
- Unexplained persistent fever
- Oral candidiasis, persistent
- Oral hairy leukoplakia
- Unexplained anemia

Other Targeted Medical Conditions:

- Diabetes mellitus
- Lipodystrophy
- Dyslipidemia
- Malaria
- Sensory peripheral neuropathy
- Hypertension
- Myocardial infarction
- Coronary artery disease, not myocardial infarction

- **Congestive heart failure, not HIV cardiomyopathy**
- **Stroke**
- **Malignancy, newly diagnosed, excluding squamous cell and basal cell cancer of the skin**
- **Renal insufficiency**
- **Liver disease**
- **Lactic acidosis**

Revision 6d Appendix IV: Sample Informed Consent Forms