

Letter of Amendment # 3 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: 30 July 2008

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 result in changes to the informed consent forms. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment.

This Letter of Amendment and any IRB/EC correspondence must be filed in the site regulatory file and in other pertinent files. Any revised informed consent forms based on this LoA must be submitted to the DAIDS/RCC Protocol Registration Office for informational purposes.

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-e. The protocol team roster has been revised to add Helen Watson who has replaced Elke Loschel on the protocol team, to delete Elke Loschel as she is no longer a member of the protocol team, to correct the email address for Leslie Cottle, the mailing address for Ying Q. Chen and the contact information for Nancy Padian.
- 2a-n. Sections 2.3.2, 2.3.3, 2.3.3.1, 2.3.3.2, 5.3.2, 7.1, Index Case Enrollment Sample Informed Consent Form, Partner Enrollment Sample Informed Consent Form, and Index Case Pregnancy Sample Informed Consent Form have been revised to indicate that the visit schedule will change as follows: three (3) monthly visits for couples at the start of the study regardless of study treatment study arm. In addition, when an Index Case initiates ART, whether at the beginning of the study or sometime during the study, both members of the couple will have a two-week follow-up visit, followed by 3 monthly visits. All other scheduled visits will be on a quarterly basis for both members of the couple.
- 3a. Section 5.3.7 has been changed to indicate that initiation of ART may begin at an interim visit, but only on a date when a monthly visit would occur.
- 4a. The trial participants recruited during the run-in are to be included in the overall final analysis. Access to their results is subject to the same guidelines as those recruited in the full study. Section 1.3 has been changed to reflect this fact.

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 ~~strike through~~; additions are indicated in **bold**.

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Revision 2a Section 2.3.2, Criteria for Switching Antiretroviral Therapy Regimen Due to Virologic Failure

Index cases in whom failure to respond is believed to be due to non-adherence, systemic illness, vaccination, or other circumstances determined by the study clinicians, will not be required to switch therapy. The starting regimen should continue and the plasma HIV-1 RNA evaluated as **clinically indicated** ~~monthly unless the study clinician advises that therapy should be changed.~~

Revision 2b Section 2.3.3, Index Case and Partner Follow-Up Visit Schedule

~~The f~~ Follow-up visits **will be** scheduled for index cases and their partners enrolled in ~~both the run-in period and full the~~ study ~~will be the same~~. It should be noted that clinical procedures and laboratory evaluations might be performed at any study visit, scheduled or unscheduled, if clinically indicated. Such procedures and evaluations will be recorded in the participant's study chart, and on applicable case report forms (CRFs).

All enrolled study participants will complete ~~monthly~~ follow-up visits throughout their participation in the study. **There will be three (3) monthly visits for couples at the start of the study regardless of study treatment arm. When an Index Case initiates ART, whether at the beginning of the study or sometime during the study, both members of the couples will have a two-week follow-up visit, followed by 3 monthly visits. All other scheduled visits will be on a quarterly basis for both members of the couple.** ~~These regular visits should be conducted every 30 days, and~~ Couples should return for the visits together. Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, visits may be completed within a defined visit window. The SSP defines the visit window associated with each visit type (2-week visit, monthly visit, etc.).

Revision 2c Section 2.3.3.1 Index Case Follow-up

Index cases will be required to report for ~~monthly~~ follow-up visits for the entire study. For those on ART, these visits will consist of obtaining **an appropriate monthly** allotment of ART drugs, completing clinical procedures and laboratory evaluations, completing adherence assessments, participating in adherence counseling, completing sexual history assessments (~~on a quarterly basis~~), and participating in couples HIV counseling with their partner. For those not on ART, visits will include completing clinical procedures and laboratory evaluations, completing sexual history assessments (~~on a quarterly basis~~), and participating in couples HIV counseling with their partner. For both arms of the study, most clinical procedures and laboratory evaluations will occur during the quarterly and yearly visits. However, once an index case is placed on their initial ART regimen, it is required that a closer safety assessment be performed two weeks after. Assessments should include hematology, liver function, and blood chemistry assessments, as well as a targeted history and physical exam. In cases where the index case stops ART, they and their respective partner should continue to be followed ~~monthly~~ and complete the required study assessments per the protocol (except the adherence assessment).

Revision 2d Section 2.3.3.2 Partner Follow-up

Partners are required to report for ~~monthly~~ **scheduled follow-up** visits to complete a sexual history assessment (~~on a quarterly basis~~), participate in couples HIV counseling, and adherence counseling (only while partner is on ART).

Revision 2e Section 5.3.2 Monthly Visits (months other than quarterly or yearly visit months)

~~Monthly study visits are required for all couples regardless of treatment arm.~~ **Three [3] monthly visits following enrollment are required for all couples regardless of study treatment arm, and an additional three [3] monthly visits for Arm 2 participants are required following initiation of ART.**

Revision 2f Section 7.1 Review of Study Design

Follow-up of the run-in period couples will continue ~~on a monthly basis~~ until the last couple enrolled into the full study has completed follow-up

Revision 2g Index Case Enrollment Sample Informed Consent Form (Monthly Study Visits)

You will come back to the clinic ~~every month~~ **for three (3) monthly visits following enrollment, and if you are in Arm 2 of the study you will come back to the clinic for three (3) monthly visits after you start taking anti-HIV drugs.** ~~during the study for a study visit.~~ These visits will last about an hour.

Revision 2h Index Case Enrollment Sample Informed Consent Form (Quarterly Study Visits)

In addition to the ~~regular~~ monthly **visit** procedures, at every 3-month visit:

Revision 2i Index Case Enrollment Sample Informed Consent Form (Additional Study Visits)

If you become sick during the study, you may be asked to return to the clinic **for additional visits more often than every month**. We will let you know if this is necessary and help you schedule any additional visits.

Revision 2j Index Case Enrollment Sample Informed Consent Form (Research-Related Injury)

The study staff will monitor your health closely while you are in this study. ~~You will have a study visit every month.~~ If you have any health problems between **follow-up** visits, please contact the study staff. If you have a medical emergency that requires immediate care, [*insert site-specific instructions*].

Revision 2k Partner Enrollment Sample Informed Consent Form (Monthly Study Visits)

You will come back to the clinic ~~every month~~ **for three (3) monthly visits following enrollment, and if you are in Arm 2 of the study you will come back to the clinic for three (3) monthly visits after your partner starts taking anti-HIV drugs.** ~~during the study for a study visit.~~ Most of these visits will last about an hour.

Revision 2l Partner Enrollment Sample Informed Consent Form (Quarterly Study Visits)

In addition to the ~~regular~~ monthly **visit** procedures, at every 3-month visit

Revision 2m Partner Enrollment Sample Informed Consent Form (Research-Related Injury)

The study staff will monitor your health closely while you are in this study. ~~You will have a study visit every month.~~ If you have any health problems between **follow-up** visits, please contact the study staff. If you have a medical emergency that requires immediate care, [*insert site-specific instructions*].

Revision 2n Index Case Pregnancy Sample Informed Consent Form (Research-Related Injury)

The study staff will monitor your health closely while you are in this study. ~~You will have a study visit every month.~~ If you have any health problems between **follow-up** visits, please contact the study staff. If you have a medical emergency that requires immediate care, [*insert site-specific instructions*].

Revision 3a Section 5.3.7 Procedures for ART Initiation Visit

The initiation of ART may ~~only begin at a regularly scheduled study visit, i.e. not~~ at an interim visit, but only on a date when a monthly visit would occur.

Revision 4a Section 1.3 Study Implementation Plan

The results of the run-in are available upon request to the HPTN 052 Protocol Chair **and the approval from the Protocol DSMB.**
