

Letter of Amendment #1 for:

HPTN 046: A PHASE III TRIAL TO DETERMINE THE EFFICACY AND SAFETY OF AN EXTENDED REGIMEN OF NEVIRAPINE IN INFANTS BORN TO HIV-INFECTED WOMEN TO PREVENT VERTICAL HIV TRANSMISSION DURING BREAST-FEEDING, VERSION 3.0, DATED 26 SEPTMEBER 2007

DAIDS Document ID 10142

Letter of Amendment Date: 16 April 2008

Instructions to the Study Sites from the Sponsor (US NIH/NIAID/DAIDS)

The following information impacts the HPTN 046 study and must be forwarded to all responsible Institutional Review Boards (IRB)/Ethics Committees (EC) as soon as possible. This Letter of Amendment must be approved by your IRBs/ECs prior to implementation.

This Letter of Amendment (LoA) includes minor changes to the informed consent forms. Participants enrolled prior to issuance of this LoA need not be re-consented with the modified consent form, unless you are otherwise instructed by your IRBs/ECs. Your IRBs/ECs are responsible for determining how study participants are to be informed of the contents of this Letter of Amendment.

This LoA and all related IRB/EC correspondence must be retained in the site regulatory file and in other pertinent files. Protocol registration approval is not required by DAIDS for Letters of Amendment.

If the full HPTN 046 protocol is amended in the future, the changes in this Letter of Amendment will be incorporated into the next version of the protocol.

Summary of Revisions and Rationale

This Letter of Amendment includes no changes in participation requirements (e.g., volume or number of blood draws). The changes included in Clarification Memorandum # 1 to Version 3.0, dated 26 February 2008 are incorporated into this LoA.

The modifications are summarized briefly below and detailed in the 'implementation' section that follows.

1. Recent unpublished data from the HPTN Network Laboratory suggest that HIV-1 diagnosis based solely on combinations of two positive EIA tests or two positive rapid tests may result in an individual being wrongly identified as infected.

Therefore, to eliminate any possibility of enrolling a mother who is not HIV-1 infected and exposing her infant to study drug, confirmation of the mother's HIV status by Western blot is now required for enrollment into HPTN 046. Note that confirmation of HIV diagnosis by Western blot has always been an option; this LoA simply makes it a requirement.

2. The Protocol Team Roster is updated.

The remaining changes were included in Clarification Memorandum # 1 to Version 3.0, dated 26 February 2008.

3. As clearly indicated throughout Version 3.0 of the protocol, the consent form included for participants enrolled under Version 2.0 (Appendix IIB) is intended for those being asked to continue in the study under Version 3.0. Those mother-infant pairs who were enrolled but not randomized under Version 2.0 are to be followed under Version 3.0 through the 3-month visit only; therefore, it is clarified that mother-infant pairs who are past the 3-month visit when the site implements Version 3.0 need not be re-consented because they are not being asked to undergo any further assessments or to continue in the study.
4. Section 4.3 specifies the infant randomization criteria and the timeframe for randomization. The target randomization day for infants is at the 6 week visit (Day 42); however, infants who meet the randomization criteria may be randomized at any time from 6 weeks (Day 42) through 8 weeks (Day 56) of life. The protocol states that abnormal lab results may be re-assessed and that if the infant meets the criteria before 8 weeks (Day 56), then the infant can be randomized. It is clarified that both abnormal lab results and clinical findings may be re-assessed within the specified timeframe to determine final eligibility for randomization. This clarification reflects no change in the eligibility criteria or time-frame for randomization.
5. Sections 6.2.2 and 6.2.3 provide instructions/criteria for resumption of dosing following a gap for open-label NVP and for study drug (blinded NVP or NVP placebo), respectively. It is clarified that, for both regimens, the instructions and criteria apply to gaps in dosing of ≥ 21 days.
6. For reporting purposes, it is clarified that a grade 4 asymptomatic laboratory adverse event is considered a serious adverse event (SAE) only if the event is *immediately* life-threatening or otherwise meets the criteria for an SAE as defined in the protocol (Section 7.0) and the Manual for Expedited Adverse Event Reporting to DAIDS. This clarification reflects no change in reporting requirements but rather serves to highlight the distinction between immediately life-threatening events (participant was actually at risk of death as the AE occurred) and potentially life-threatening events (participant may have been at risk of death *if* the condition had been worse). Note that this applies to infants enrolled under Version 2.0 or Version 3.0 of the protocol.

Implementation

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 strikethrough; additions are indicated in **bold**.

- 1) Mother's eligibility criteria: Requirement for Western blot confirmation

Section 2.1, Maternal Screening, Enrollment and Follow-Up, third paragraph, second sentence:

Women identified as HIV-infected through standard of care testing ~~women~~ who provide informed consent may be screened for the study at any time during the third trimester of pregnancy or on or before Day 7 after birth. At screening women will undergo medical history and physical, as outlined in the Study Specific Procedures (SSP) Manual and will undergo one blood draw for CBC with differential, CD4+ cell count, **confirmatory HIV diagnostic testing**, stored plasma for later NVP resistance, HIV-1 RNA PCR testing.

Section 4.1, Maternal Eligibility Criteria, the fourth bullet will be amended as follows:

- HIV-infected, as evidenced by ~~2 positive EIA's; or~~ **at least 1 positive EIA and one positive WB or at least 1 positive rapid test and 1 positive WB;** ~~or 2 separate positive rapid tests (WHO acceptable diagnostic HIV-1 infection criteria for adults)~~

Section 5.1, Screening and Follow-up Maternal Evaluations; Section 5.1.1 Maternal Eligibility Evaluations: third trimester of pregnancy/on or before Day 7 postpartum, with the "Note" under Clinical Evaluations moved under Laboratory Evaluations and modified as follows:

Clinical Evaluations and Instructions

- ~~Documentation of HIV-infected status*~~
- Infant feeding options counseling
- Study informed consent
- Specimen storage consent (optional)
- Demographics
- Confirmation of intent to breastfeed
- Medical history
- Physical exam

Laboratory Evaluations

- ~~Confirmatory HIV test (if needed)~~
- **HIV-1 EIA or rapid test, if needed***
- **Western blot***
- CBC with differential
- CD4+ cell count
- Plasma storage for HIV-1 RNA PCR and NVP resistance testing
- Dried blood spot storage for back-up testing

*Note: If documented ~~confirmation~~ **evidence** of the mother's HIV status (as evidenced by ~~2 positive EIA's; or 1 positive EIA or 1 positive rapid test, and 1 WB; or 2 separate positive rapid tests~~) is not available as part of standard of care at the study clinic, then ~~confirmatory~~ **this** testing will be performed after study informed consent has been obtained and prior to enrollment (~~infant randomization~~). **Confirmatory testing by Western blot is required after informed consent is obtained, regardless.**

APPENDIX I A, SCHEDULE OF MATERNAL EVALUATIONS,

Rows 1 and 2 in column 1 are modified as follows:

~~Documentation of HIV Status~~ **HIV-1 EIA or rapid test, if needed**
~~Confirmatory HIV test (if required)~~ **Western blot**

APPENDIX II A, Sample Study Consent Form for Initial Enrollment Under Protocol Version 3.0:

Screening Procedures: If you agree to take part in this study and sign the informed consent form, we will first need to find out if you and your baby are able to join. This will include asking you some questions about your health and doing a physical examination. Some people may not be able to join the study due to information learned during the screening. You will also be asked to give a blood sample (about 10 ml, which is less than one tablespoon) to check your health and to be stored for later HIV-related tests. ~~If Your previous HIV test result has not yet been~~ **will be confirmed by at least one other second HIV test;** we will counsel you about this and use some of the blood sample you gave to do ~~another the~~ **HIV testing. If so, You** will need to come back to the clinic to find out the results of your HIV tests and receive counseling. If the ~~second latest~~ **HIV test result** is negative, you and your baby cannot join the study. If the ~~second latest~~ **HIV test result** is not negative but is also not positive, you will be offered more HIV counseling and testing.

2) Protocol Team Roster Changes

Francis Mmiro will be removed as the Ugandan Investigator.

Philippa Musoke will be added as the Ugandan Investigator, as follows:

Philippa Musoke, MBChB
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P.O. Box 23491
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3) Applicability of Consent Form for Participants Enrolled but Not Randomized under Version 2.0

Section 2.1, Maternal Screening, Enrollment and Follow-up, sub-section entitled "Version 2.0 Maternal Follow-up": The following text in bold will be added to last paragraph in this section:

Mothers of infants enrolled under Version 2.0 of the protocol and were not randomized (including those enrolled on or after 10 August 2007) that consent for continued participation will be followed according to the study schedule described above through the Month 3 visit only and will then be terminated from the study. **Mothers of infants who were enrolled but not randomized under Version 2.0 and who are past the Month 3 visit when the site implements Version 3.0 need not be re-consented because they are not being asked to continue in the study. Instead, at the next visit, the study staff will explain to the mother that her and her infant's participation in the study is complete and document this in the participants' source records; no further assessments are to be undertaken.**

Section 2.3, Version 2.0 Infant Follow-up: The following text in bold will be added to last paragraph in this section:

Infants enrolled under Version 2.0 of the protocol who were not randomized (including those enrolled on or after 10 August 2007) and whose mothers consent for continued participation will be followed according to the study schedule described above through the Month 3 visit only and will then be terminated from the study. **Mothers of infants who were enrolled but not randomized under Version 2.0 and who are past the Month 3 visit when the site implements Version 3.0 need not be re-consented because they are not being asked to continue in the study. Instead, at the next visit, the study staff will explain to the mother that her and her infant's participation in the study is complete and document this in the participants' source records; no further assessments are to be undertaken.**

4) Randomization Criteria

Section 4.3 Infant Randomization Criteria: The following text in bold will be added and the text that is marked through will be removed from the first note following the criteria:

Note: Abnormal lab **and clinical results findings** as specified above may be reassessed and, if the infant meets all the criteria for randomization on or before 8 weeks (Day 56), the infant can be randomized.

5) Gaps in Dosing

Section 6.2.2, Conditions for Exclusion from Subsequent Doses of Open-Label NVP (through 6 weeks (42 days) of life): The text in bold will be added to the existing note.

Note: Infants with a gap in dosing **of 21 days or more** after initiation of open-label NVP until age 6 weeks must have a negative HIV DNA PCR result (or quantitative RNA PCR) on a specimen obtained at the study visit when the gap was identified or within the prior three weeks (≤ 21 days) and must have been exposed to breast milk within the last 30 days or dosing cannot be resumed. Resumption of open-label NVP 6-week regimen is to be at the dose appropriate for the infant's age.

Section 6.2.3, Initial and Subsequent Study Drug Dosing Following Randomization: The text in bold will be added to the existing note.

Note: Randomized infants who did not initiate study drug or with a gap in dosing **of 21 days or more** after initiation must have a negative HIV DNA PCR result (or quantitative RNA PCR) on a specimen obtained at the study visit when the non-initiation or gap was identified or within the prior three weeks (≤ 21 days) and must have been exposed to breast milk within the last 30 days or dosing cannot be started or resumed. Initiation or resumption of study drug is to be at the dose appropriate for the infant's age.

6) Reporting of Grade 4 Adverse Events

Appendix V, HPTN 046 Adverse Event Reporting and Documentation Requirements: The following note will be added after the footnotes to the table:

Note: A grade 4 asymptomatic laboratory adverse event is considered a serious adverse event (SAE) only if it is *immediately* life-threatening or otherwise meets the criteria for an SAE as defined in this protocol (Section 7.0) and the Manual for Expedited Adverse Event Reporting to DAIDS.