

Letter of Amendment #1 to
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 Breastfeeding
Version 2.0, dated 22 May 2005

(DAIDS DOCUMENT ID 10142)

Letter of Amendment Date: 14 June 2007

Instructions to the Study Site from the Sponsor (Division of AIDS)

The following information impacts the HPTN 046 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 your IRB/EC before implementation.

This Letter of Amendment (LOA) includes no changes to the informed consent forms; however, your IRB/ECs are responsible for determining whether and 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

The modifications included in this Letter of Amendment have no impact on participant safety and do not impact the risk-to-benefit ratio of study participation or the participation requirements. No modifications to the informed consent forms are included in this Letter of Amendment.

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

1. In order to best manage incidences of neutropenia and anemia, which may occur at an increased rate in the HPTN 046 study population and to avoid the unnecessary withholding

of study product, the Toxicity Management Procedures table in Appendix IV of the protocol has been updated with specific instructions for both of these conditions.

2. The procedure for the storage of blood has been specified to include dried blood spot storage for both mothers and infants, in addition to plasma storage. Dried blood spots will be stored for back-up purposes for protocol specified tests only. This will not require any change in the volume of blood collected.
3. To properly execute the existing Quality Control Plans of the Network Laboratory, cell pellets from DNA PCR assays will be stored. This will not require any change in the volume of blood collected.
4. To conform to the current Network Laboratory policy, the Quality Assurance retesting of 5% of enrolled women for the presence HIV antibody to confirm HIV-1 infection will be changed to 10%.
5. The maternal HIV infection eligibility criterion has been modified to reflect that 1 positive rapid HIV test and 1 positive western blot is acceptable as evidence of HIV-infection
6. The definition of infant age has been clarified to provide guidance for the time points at which infants can receive study medication based on the Infant Dosing Table in the Schema and Section 6.2. Age will be defined using a rounding rule, similar to those used for weight, specifying that infants will be considered to be the appropriate age for a dose adjustment if they are no more than one week below the target age, except at two weeks of age when the dose is escalated. Infants will be eligible for the two week dose escalation at only two days prior to the target age. There are no safety concerns associated with adjusting the dose of infants who are one week under the target age from a PK standpoint, particularly given the fact that that there will be much variation in weight, and after the 2-week dose escalation the doses are adjusted for growth with the goal of keeping the dose per kg relatively constant. The dose adjustments are very small and the concentrations are much lower than therapeutic doses.
7. To clarify the administration of study drug and syringes to mothers and to provide for the safe follow-up of infants, Section 6.2 has been modified to specify the maximum amount of study drug and syringes that may be dispensed at one time. This clarification also specifies that mothers who inform the site that they will not be available during the next study window will not receive any study product until they again return to the clinic.
8. The instructions for initiation of study drug on Day 5 after birth (± 2 days) have been clarified, and instructions to consult the Protocol Safety Review Team (PSRT) with any concerns or questions about introduction or resumption of study drug dosing have been added.
9. It is clarified that normal variations in typical neonatal conditions that are not regarded as unfavorable are not considered reportable adverse events as defined in Section 7.0; examples include clinical findings such as milia, miliaria and newborn peeling and laboratory findings such as slightly elevated or low monocyte, basophil or MCH counts or elevated platelet, neutrophil or lymphocyte counts, as these are not toxicities.
10. Grade 3-A2 of the Supplemental Table for Grading the Severity of Cutaneous/Skin Rash/Dermatitis, Malnutrition and Fever which describes skin rash, is modified from

“fever, >39°C” to “Grade 2 fever.” This clarification allows for the original intent of this constitutional finding regardless of how the temperature is measured (axillary or rectal).

11. To correct an inconsistency in the protocol, the units describing the target nevirapine concentration levels “micrograms” (mcg) is replaced by “nanograms” (ng). The majority of references to the concentration level throughout the protocol include the correct unit.
12. The Protocol Team Roster is updated.
13. All references to the Central Laboratory (CL) in the protocol are updated to Network Laboratory (NL).

Implementation of Modifications

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. Neutropenia and Anemia Management

Appendix IV, Toxicity Management Procedures, the following will be added:

CONDITION	STUDY DRUG USE	FOLLOW-UP AND MANAGEMNT
NEUTROPENIA AND ANEMIA MANAGEMENT		
Grade 1 or Grade 2 neutropenia or anemia: regardless of relatedness	Continue study drug	
Grade 3 neutropenia or anemia: possibly related, probably not related or not related	Continue study drug	Repeat assessment within 5-7 days. If repeat assessment is Grade 2 or less, continue study drug. If repeat assessment confirms a Grade 3, continue study drug at least until consultation with the Protocol Safety Review Team. The Protocol Safety Review Team will determine the frequency of repeat assessment and provide instructions for further study drug dosing.
Grade 3 neutropenia or anemia: probably related or related; or any Grade 4 neutropenia or anemia that is <u>not</u> immediately life threatening	Hold	Repeat assessment within 5-7 days. If repeat assessment is Grade 2 or less, study drug may be restarted. If repeat assessment is Grade 3 or higher, study drug is not to be re-started without consultation with and permission from the Protocol Safety Review Team.
Grade 4 neutropenia or anemia that is immediately life threatening	Immediate and permanent discontinuation	
EVENTS OTHER THAN HEPATIC TOXICITY, NEUTROPENIA AND ANEMIA, OR RASH MANAGEMENT		

2. **Dried Blood Spot Storage**

Section 2.1, Maternal Screening, Enrollment and Follow-up, paragraph 2, the following sentence will be added:

Dried blood spots will be stored, for back-up testing, at each maternal visit.

Section 2.2, Infant Randomization and Follow-up, paragraph 2, the following sentence will be added:

Dried blood spots will be stored at birth (prior to enrollment/randomization and on or before Day 3 after delivery), 2 and 6 weeks, 3, 6, 9, 12, and 18 months for back-up testing.

The bullet

- **Dried blood spot storage for back-up testing**

will be added to the following sections:

- *Section 5.1.1, Maternal Eligibility Evaluations: third trimester of pregnancy/on or before day 3 postpartum, Laboratory Evaluations*
- *Section 5.1.2, Maternal Labor and Delivery Evaluations: as close to delivery as possible but on or before day 3 after delivery, Laboratory Evaluations*
- *Section 5.1.3, Maternal Follow-up Evaluations, Laboratory Evaluations (2 and 6 weeks and 3, 6, and 12 months) and Laboratory Evaluations (18 months)*
- *Section 5.2.1, Infant Evaluations Prior to Enrollment/Randomization (on or before Day 3 of life), Laboratory Evaluations*
- *Section 5.3, Maternal Evaluation in the Case of Early Withdrawal*
- *Section 5.4, Infant Evaluations in the Case of Treatment Discontinuation or Study Withdrawal*

Section 5.2.2, Follow-up Infant Evaluations, Laboratory Evaluations, the following bullet will be added:

- **Dried blood spot storage for back-up testing (at 2 and 6 weeks, 3, 6, 9, 12, and 18 months)**

Appendix I A, Schedule of Maternal Evaluations, Dried blood spot storage will be added under the Evaluations column and marked at all visits

Appendix I B, Schedule of Infant Evaluations, Dried blood spot storage will be added under the Evaluations column and marked at Enrollment, 2 and 3 weeks, 3, 6, 9, 12, and 18 months

3. Cell Pellet Storage

Section 5.2.1, Infant Evaluations Prior to Enrollment/Randomization (on or before Day 3 of life), Laboratory Evaluations, the 3rd bullet will be amended as follows:

- Real-time Roche Amplicor HIV-1 DNA PCR testing (Note: Quantitative HIV-1 RNA PCR may be used if HIV-1 DNA PCR is not available). **Cell pellet from HIV-1 DNA PCR assay will be stored for quality assurance testing.**

Section 5.2.2, Follow-up Infant Evaluations, Laboratory Evaluations (at 2, 4, 6, and 8 weeks and 3, 6, 9, 12, and 18 months), the 3rd bullet will be amended as follows:

- Real-time Amplicor HIV-1 DNA PCR testing (at 2 and 6 weeks and 3,6, 9, and 12 months only). If positive, repeat test on a second sample on or before the participant's next scheduled visit for confirmation, see section 8.6.1. (Note: Quantitative HIV-1 RNA PCR may be used if HIV-1 DNA PCR is not available.) **Cell pellet from HIV-1 DNA PCR assay will be stored for quality assurance testing.**

Section 5.4, Infant Evaluations in the Case of Treatment Discontinuation or Study Withdrawal, in the 2nd section, the 6th bullet will be amended as follows:

- Roche Amplicor HIV-1 DNA PCR **and cell pellet storage.**

In the third section, the 3rd bullet will be amended as follows:

- Roche Amplicor HIV-1 DNA PCR **and cell pellet storage.**

4. Network Laboratory Quality Assurance Policy

Section 10.3, Quality Control and Quality Assurance Procedures, 2nd paragraph, 3rd sentence will be amended as follows:

In addition, ~~5%~~ **10%** of women enrolled will be retested by the CL for HIV antibody in order to confirm HIV-1 infection.

5. Maternal Eligibility Criteria

Section 4.1, Maternal Eligibility Criteria, the 4th bullet will be amended as follows:

- HIV-infected, as evidenced by 2 positive EIAs; or 1 positive EIA **or rapid test** and 1 positive WB; or two separate **positive** rapid tests (WHO acceptable diagnostic HIV-1 infection criteria for adults)

6. Definition of Infant Age

In the SCHEMA and Section 6.2, Treatment Dose and Administration, the following note will be added below the dosing tables:

Note: Infants will be considered to be the appropriate age for dose adjustment if they are no more than one week below the target age, except at two weeks of age. Infants will be eligible for the two week dose escalation at only two days prior to the target age.

7. Study Drug and Syringe Dispensing

Section 6.2, Treatment Dose and Administration, the following will be added:

Mothers will receive syringes and instructions for dosing the oral suspension to their infants. **Mothers will receive at least enough study drug and syringes to dose their infant until the next scheduled visit. Clinic staff may request additional study drug and syringes in the event that the mother cannot return to the clinic on the infant's scheduled visit date but can return within the infant's visit window. If a mother informs the site staff that they will not be able to return for a follow-up visit during the entire next visit window, the mother will not receive any further study product until the baby is able to return to the clinic. Site staff may not authorize dispensation of any additional supply of study drugs or oral syringes that would be used in the event of a missed visit window because infants need to be seen to be properly evaluated for possible toxicities. Details of this distribution can be found in the SSP manual.** The study drug regimen will be based on infant age...

8. Dose Initiation and Breastfeeding

Section 6.2.1, Conditions for Exclusion from Initial Study Drug Dosing, will be amended as follows:

Note: Mothers will be instructed to begin administration of the study drug to the infant on Day 5 after birth (± 2 days), with the day of birth considered Day 0. If at a subsequent study visit, the study staff learn that administration of the study drug was not begun within this timeframe and the infant continues to meet the dosing criteria specified above **and has been exposed to breast milk within the last 30 days**, the procedures below will be followed:

- If within four weeks (≤ 28 days) of the Day 5 target: The mother will be instructed to begin dosing as soon as possible at the appropriate level for the infant's age.
- If more than four weeks (> 28 days) after the Day 5 target: The mother will be instructed to begin dosing as soon as possible at the appropriate level for the infant's age *only if* an HIV DNA PCR result from a specimen drawn at

the current visit or within the previous two weeks is negative. (Note: Quantitative HIV-1 RNA PCR may be used if HIV-1 DNA PCR is not available.)

Note: Concerns or questions about introduction or resumption of study drug dosing in unusual cases should be directed to the PSRT, which will determine how the situation is to be handled.

9. **Normal Variations in Typical Neonatal Conditions**

Section 7.0, Safety Monitoring and Adverse Event Reporting, the 1st paragraph will be amended as follows:

An adverse event (AE) is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which may or may not have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. Study participants will be instructed to contact the study clinician to report any AEs their infants may experience. **Normal variations in typical neonatal conditions that are not regarded as unfavorable are not considered adverse events as defined above; examples include clinical conditions such as milia, miliaria and newborn peeling and laboratory findings, which are not gradable events per the DAIDS Toxicity Table, such as slightly elevated or low monocyte, basophil or MCH counts, or elevated platelet, neutrophil or lymphocyte counts.**

10. **Toxicity Grading of Grade 3-A2 Skin Rash**

Appendix III, Supplemental Table for Grading the Severity of Cutaneous/Skin Rash/Dermatitis, Malnutrition and Fever, the Grade 3 column will be amended as follows:

A. Diffuse erythematous macular or maculopapular cutaneous eruption or moist desquamation with or without pruritis together with any of the following constitutional findings considered related to the drug:

1. 5 x ULN AST, ALT or 2 x baseline if baseline > ULN
2. ~~fever, >39°C~~ **Grade 2 fever**
3. blistering and/or vesiculation of cutaneous eruptions
4. any site of mucosal lesions; OR

11. **Nevirapine Concentration Level Units**

List of Abbreviations and Acronyms will be amended as follows:

ng nanogram

The terms “micrograms” or “mcg” will be replaced by “ng” in the following sections:

- *Section 1.2, Rationale for Extended Regimen of Infant NVP to Prevent MTCT, 3rd paragraph, 2nd sentence*
- *Section 1.3.1, Pharmacokinetics of Intrapartum/Neonatal NVP, 1st paragraph, 1st sentence and 2nd paragraph*
- *Section 1.5, HIVNET 023: Safety and Pharmacokinetics of Extended NVP Regimen, 1st paragraph, 2nd sentence*

12. **Protocol Team Roster Changes**

Susan Eshleman’s role will be changed from Protocol Virologist to HPTN Network Lab Representative and Protocol Virologist.

Sarah Dawson’s role will be changed from Central Laboratory Representative to Network Laboratory Quality Assurance Coordinator (QAC).

Philip Andrew will replace Bethany Freeman as Protocol Specialist as follows:

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13. **Central Laboratory Updated to Network Laboratory**

Throughout the entire protocol Central Laboratory (CL) will be replaced by **Network Lab (NL)**