

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

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)

THE AMENDED PROTOCOL IS IDENTIFIED AS:

Version 3.0, 26 September 2007

IND # 72,592

Summary of Revisions and Rationale

The modifications included in this protocol amendment and the associated rationale are summarized briefly below. HPTN 046 study investigators will submit this Summary of Changes and the corresponding protocol Version 3.0 to all relevant regulatory authorities and Institutional Review Boards/Ethics Committees (IRBs/ECs) for approval. Upon completion of protocol registration procedures with the DAIDS Regulatory Compliance Center, Version 3.0 of the protocol may be implemented.

The most significant modifications included in this amendment are related to **replacement of the placebo control with a regimen of nevirapine (NVP)** given to infants through 6 weeks (42 days) of life, as recommended by the NIAID Data and Safety Monitoring Board. This recommendation was based on review of preliminary results of a pre-planned combined analysis of three other studies (collectively known as the Six Week Extended Nevirapine (SWEN) study) which showed that nevirapine given through 6 weeks (42 days) of life to breastfeeding infants in India, Uganda and Ethiopia significantly reduced the risk of HIV transmission from mother to infant at six weeks and was associated with significantly lower mortality rates at six weeks and six months of age. Some immediate changes in HPTN 046 were implemented on 10 August 2007 as directed in a set of documents of the same date which were developed by the sponsor and study team leadership and submitted to the IRBs/ECs and regulatory authorities, including a Study Memorandum, a Participant Letter, Instructions to the Site Investigators and an Executive Summary of the preliminary SWEN study results. This full amendment from Version 2.0 to Version 3.0 reflects the long-term plan for and re-design of the study necessitated by the SWEN study findings.

Changes included in Letter of Amendment # 1 to Version 2.0, dated 14 June 2007, were also incorporated into the protocol text in this amendment as noted below.

The modifications are summarized as follows:

- The background and rationale sections have been updated with the available details of the SWEN study, other relevant trials (e.g., SIMBA, MITRA and MASHI) and new WHO guidelines on infant feeding. Seven new references were added.
- The purpose of the study has been revised to state that it is “to evaluate the efficacy and safety of an extended regimen of nevirapine from 6 weeks to 6 months ... compared with placebo among infants provided nevirapine for the first 6 weeks (through Day 42) of life and are HIV-uninfected at age 6 weeks”. This is consistent with the approach included the original protocol in which the stated purpose was evaluation of 6 months of NVP compared to placebo and reflects the fact that for evaluation purposes the 6 week regimen is in the background, crossing both arms of the study.
- All infants enrolled under Version 3.0 of the protocol will be provided NVP through six weeks (Day 42) of life; those eligible will be randomized at the 6-week visit to receive either active NVP or NVP placebo daily through six months or until cessation of breastfeeding, whichever is earliest.
- Infants enrolled under Version 3.0 of the protocol who are not randomized for any reason will be followed according to the study schedule through the Month 3 visit only and will then be terminated from the study. Their mothers will have no further assessments done and be terminated immediately.
- All infants who were enrolled and randomized under Version 2.0 of the protocol will remain in the study and be followed for 18 months according to the study schedule along with their mothers;
 - Those who were either randomized to the placebo arm and over six weeks (≥ 43 days) of age as of 10 August 2007 or randomized to the NVP arm (regardless of age) will continue the dosing regimen to which they were randomized (NVP or NVP Placebo);
 - Those who were randomized to the placebo arm and six weeks of age or less as of 10 August 2007 were unblinded and offered open-label NVP through Day 42 of life (as communicated previously).
- Infants enrolled under Version 2.0 on or after 10 August 2007 were not randomized but were offered open-label NVP through Day 42 of life (as communicated previously). Those whose mothers consent for continued participation will be followed according to the study schedule through the Month 3 visit only and will then be terminated from the study along with their mothers.
- The term “study drug” is defined as the regimen to which infants are randomized (NVP or NVP Placebo through six months or until cessation of breastfeeding, whichever is earliest) and is used throughout the protocol to distinguish this regimen from the “open-label NVP” regimen now given to all infants through six weeks (42 days) of age.
- The treatment regimen tables in the Schema, in Section 1.6 (Rationale for Daily Dosing) and in Section 6.0 (Study Treatment) have been updated to reflect NVP dosing to all enrolled infants through 6 weeks (42 days) of age and the randomized study drug regimen (NVP or NVP Placebo) thereafter. The study treatment regimen and dose adjustment schedule otherwise remain unchanged, with two minor exceptions, which are also reflected in the revised tables:

- The dose adjustment previously designated for 4 weeks of age, has been changed to 5 weeks to correspond with the change in the visit schedule (replacement of the 4 week visit with the 5 week visit).
 - The 6 week dose adjustment cannot be started before randomization and Day 43 of life.
- The window for enrollment has been extended through 7 days of life (from 3 days), with a negative DNA PCR and normal ALT and CBC results now required prior to enrollment. In Version 2.0, these lab results were not required prior to enrollment because the three-day enrollment window did not allow sufficient time to guarantee availability. With randomization occurring later in Version 3.0 (see bullet immediately below), there is sufficient time to obtain the results and to exclude infants who are infected at birth or otherwise not eligible for open-label NVP prior to enrollment and dispensing of the drug.
- A standard principle of trial design is to randomize at a time as proximal as possible to the point at which the strategies being assessed differ. Therefore, randomization to one of the two study arms (NVP or NVP Placebo) has been moved from birth to the 6-week visit, as all enrolled infants will be provided nevirapine for the first six weeks (42 days) of life. Randomization of eligible infants is targeted for the 6-week visit and must occur at or before the 8 week visit (Day 56); a negative HIV DNA PCR from the Week 5 visit is required. Randomization will be stratified across only two levels of maternal ART exposure at the point of randomization (receiving ARV for HIV treatment or not receiving ARV for HIV treatment); the third level with ART for PMTCT applied in Version 2.0 is no longer relevant, given the movement of randomization to six weeks.
- The criteria for infant enrollment (Section 4.2), for initiation and continuation of the 6 week open-label NVP dosing regimen (Sections 6.2.1 and 6.2.2), for infant randomization (Section 4.3) and for initiation and continuation of the post-randomization study drug regimen (NVP or NVP placebo for 6 months or through cessation of breastfeeding) (Section 6.2.3) have been modified slightly to reflect separation of the enrollment and randomization time points and the fact that there are two different infant dosing periods/regimens: one open-label and to begin at/after enrollment at Day 3-7 after birth and the other blinded and to begin post randomization at 6 weeks (NVP or NVP Placebo). For consistency, it is now specified that a negative HIV DNA (or RNA) PCR on a specimen obtained within the previous 21 days is required for initiation or resumption of dosing following a gap in either dosing periods/regimens. As specified in Letter of Amendment # 1 to Version 2.0, instructions for delayed initiation of study drug regimens have been further 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.
- The sample size has increased modestly from enrollment of approximately 1576 mother-infant pairs to approximately 1670 mother-infant pairs, with the target number to be randomized increased from 1450 to 1500 based on findings from the SWEN study, replacement of the control arm, and movement of the randomization time point. In addition, approximately 250 mother-infant pairs enrolled under Version 2.0 of the protocol will be followed under Version 3.0. Sections 8.1 (Study Design), 8.3 (Accrual Follow-up and Sample Size) and 8.4 (Random Assignment and Stratification) have been updated to reflect the design changes described above and to include the new power calculations. Minor changes were made in Sections 8.2 (Endpoints) and 8.6.1 (Primary Analyses) to reflect that the primary efficacy endpoint is HIV infection at 6 months among infants HIV-uninfected at *6 weeks* (rather than at birth), and Section 8.6.2 has been changed entirely to focus on analysis of the Version 2.0 Cohort rather

than general secondary study analyses (which have been moved to a separate analysis plan external to the protocol).

- The Week 4 study visit for infants has been changed to occur at Week 5, with one additional real time laboratory test (CBC at Week 5), movement of the real time HIV DNA PCR from Week 6 to Week 5 and storage of plasma added at Weeks 5 and 8. As specified in Letter of Amendment #1 to Version 2.0, dried blood spots will be stored both mothers and infants at each scheduled blood draw time point (in addition to plasma) for back-up of protocol specified tests only and cell pellets will be stored for infants at each scheduled blood draw time point (with the exception of 18 months) for back-up PCR and quality assurance testing. The changes in infant evaluations are included in Section 2.2 (Infant Enrollment, Randomization and Follow-up), Section 5.2.2 (Infant Follow-up Evaluations) and Appendix I B (Schedule of Infant Evaluations) and the additional blood spot storage for mothers is specified in Sections 2.1 and 5.1 and Appendix IA (Schedule of Maternal Evaluations). The visit schedule otherwise remains unchanged; no additional blood draws are introduced; and no change in specimen volume at any time point is required.
- The informed consent form for enrollment (Appendix II A) has been updated to reflect the changes described above for mothers and infants to be enrolled under Version 3.0 of the protocol.
- A new consent form has been added (Appendix II B) for obtaining consent for continued participation in the study from mothers of infants enrolled under Version 2.0 of the protocol.
- Section 2.4 (Diagnostic Testing to Determine HIV Infection) has been updated to reflect use of the latest available version of the assays.
- It is clarified in Section 7.0 (Safety Monitoring and Adverse Event Reporting) that the drug that must be considered in determining relationships of AEs in HPTN 046 is the daily open label nevirapine regimen begun in infants 3 to 7 days after birth and given for 6 weeks (42 days) of life and the blinded daily NVP or NVP Placebo regimen begun after randomization at 6 weeks of life. Because the duration of follow-up for infants enrolled but not randomized is shorter than for those randomized as specified above (3 months vs. 18 months), the adverse event (AE) reporting period for these infants has been defined. Also, pre-existing conditions are now defined as those occurring prior to enrollment (rather than before randomization). As specified in Letter of Amendment # 1 to Version 2.0, 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. The AE reporting requirements/procedures otherwise remain unchanged.
- A section on co-enrollment into other studies was added (Section 5.9).
- Updated information was added regarding access to care and treatment at the study sites (Section 9.3, Access to HIV-Related Care).

The following additional changes which were specified in **Letter of Amendment #1 to Version 2.0, dated 14 June 2007**, were also incorporated into the revised protocol.

- 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 table of Toxicity Management Procedures in Appendix IV of the protocol was updated with specific instructions for both of these conditions.
- To conform to the updated HPTN Laboratory policy, quality assurance re-testing of enrolled women for the presence HIV antibody to confirm HIV-1 infection was increased to 10% (from 5%).
- The maternal HIV infection eligibility criterion has been modified to reflect that one positive rapid HIV test and one positive western blot is acceptable as evidence of HIV-infection.
- The definition of infant age was clarified to provide guidance for the time points at which infants can receive study product based on the Infant Dosing Table in the Schema and Section 6.2. Age is 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 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.
- For clarification and participant safety, Section 6.2 (Treatment Dose and Administration) has been modified to specify the maximum amount of study product 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.
- 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 reflects the original intent of this constitutional finding regardless of how the temperature is measured (axillary or rectal).

Additional minor changes include the following:

- The DAIDS Document ID Number and IND number were added to the face page.
- It is acknowledged on the face page, in the schema and Section 4.0 that participating sites may include other DAIDS Clinical Trials Sites in addition to or instead of the four originally planned.
- The protocol team roster was updated to reflect changes in contact information and replacement of one of the protocol statisticians, one of the protocol operations coordinators and one of the protocol specialists.
- The Table of Contents was updated to reflect the new pagination.
- The List of Acronyms was updated to include new entries introduced in this version of the protocol.
- The reference numbers throughout the protocol were updated to accommodate addition of the new references.
- ZDV was replaced with AZT throughout the background.

- To correct an inconsistency in the protocol, the units describing the target nevirapine concentration levels “micrograms” (mcg) was replaced with “nanograms” (ng).
- References to the Central Laboratory (CL) in the protocol were updated to Network Laboratory (NL).
- Minor wording changes were made throughout for clarification or correction; for example, the term “infant NVP” was eliminated.

Implementation of Modifications

The following changes have been incorporated into the text of Version 2.7 of HPTN 046 (Draft of Version 3.0, dated 20 September 2007).

- The following sections of the Schema have been updated.

Purpose

Study population

Study Size

Stratification

Study Duration, this section has also been moved.

Treatment Regimen

Primary Objectives

Study Sites

- The modifications to the text in Section 1.0 are shown in Appendix A of this Summary of Changes.
- Section 2.0 has been modified as follows:

Paragraph 1, the purpose has been updated

Paragraph 2 has been broken into two paragraphs and updated

Paragraph 3, the windows for infant enrollment has been updated

Paragraph 3, the timeframe for initiation of open-label NVP has been specified

Paragraph 3, the timeframe for obtaining a negative HIV test prior to randomization has been specified

Paragraph 3, the window for infant randomization has been updated

Paragraph 3, the open-label NVP dosing regimen has been specified

Paragraph 3, the study drug dosing regimen is updated

Paragraph 3, terms and definitions for “open-label NVP” and “study drug” have been specified

Paragraph, the follow-up schedule for infants determined to be HIV-infected has been updated

Paragraph 4, the stratification for randomization has been updated

Paragraph 5, the target enrollment and randomization number has been updated

Paragraph 5, the follow-up schedule for infants enrolled but not randomized has been specified.

Paragraph 6, the enrollment, follow-up and dosing schedules for participants enrolled in Version 2.0 of the protocol have been specified.

- Section 2.1 has been modified as follows:

Paragraph 3, the window for maternal screening and enrollment has been updated

Paragraph 3, dried blood spot storage has been added

The procedure for evaluating adherence has been moved to Section 2.2

The follow-up schedule for mothers of non-randomized infants has been specified

The follow-up schedule for mothers enrolled in Version 2.0 of the protocol has been specified

- Section 2.2 has been modified as follows:

Paragraph 1, the window for enrollment has been updated

Paragraph 1, the open-label NVP dosing regimen has been specified

Paragraph 2, the window for randomization has been updated

Paragraph 2, the study drug dosing regimen has been updated

Paragraph 3, the procedure for evaluating adherence from Section 2.1 has been added

Paragraph 4, the Week 4 study visit for infants has been changed to occur at Week 5 and, the schedule for physical examinations and medical histories and laboratory evaluations have been updated accordingly

Paragraph 4, CBC has been added at 5 weeks

Paragraph 4, the schedule for plasma storage has been moved from paragraph 5 and plasma storage has been added at 5 and 8 weeks

Paragraph 4, dried blood spot storage has been added

Paragraph 5, the schedule for real-time HIV-1 DNA PCR testing has been updated

Paragraph 5, cell pellet storage has been added

Paragraph 5, instruction for permanently stopping open-label NVP dosing in non-randomized infants determined to be HIV-infected has been specified

Paragraph 5, the follow-up schedule for non-randomized infants determined to be HIV-infected has been specified

The follow-up schedule for infants enrolled but not randomized has been added to the end of this section.

- Section 2.3 has been added and includes the follow-up schedule for both infants randomized in Version 2.0 of the protocol and infants enrolled, but not randomized in Version 2.0 of the protocol

- Section 2.4, the availability of PCR kits has been updated

- Section 3.1, the primary objective has been updated

- Section 4.0 has been modified as follows:

Paragraph 1, the target number of enrolled participants and the target number of randomized participants have been updated

Paragraph 1, the study sites have been updated

Paragraph 1, the study size of participants enrolled in Version 2.0 has been specified

- Section 4.1 has been modified as follows

Maternal Eligibility Criteria, the screening and enrollment window has been updated
Maternal Eligibility Criteria, the tests acceptable for confirmatory HIV testing have been updated

- Section 4.2 has been modified as follows

Section 4.2 has been modified to specify the criteria for enrollment in the study. Section 4.3 has been added and will specify the criteria for randomization.

First sentence, the window for enrollment has been updated

The inclusion/exclusion criteria are unchanged from the infant randomization criteria specified in Version 2.0 except where noted below:

- A negative HIV-1 DNA PCR result from a specimen obtained at birth has been made an inclusion criterion. The criterion of obtaining a specimen at birth has been removed
- Certain current ALT and hematologic abnormalities have been made exclusionary. The criterion of obtaining a specimen for these lab tests at birth has been removed.

Last paragraph, the randomization procedures in the case of multiple births has been moved to Section 4.3

- Section 4.3 has been modified as follows

Paragraph 1, the target randomization day and window for randomization have been specified.
Paragraph 1, last sentence, infants who have initiated open-label NVP are eligible for randomization has been specified.

The inclusion/exclusion criteria are unchanged from the infant randomization criteria specified in Version 2.0 except where noted below:

- The criterion, born to an HIV infected women who has consented and is eligible to take part in the study has been removed. This remains a criterion for enrollment in Section 4.2
- The criterion, birthweight of at least 2000 gm has been removed. This remains a criterion for enrollment in Section 4.2
- The criterion a negative HIV-1 DNA PCR result at 5 weeks has been added. The criterion for obtaining a specimen at birth for HIV-1 DNA PCR testing has been removed.
- The criterion infant required permanent discontinuation of open-label NVP given during the first 42 days of life has been made exclusionary
- The criterion an infant never initiated the open-label NVP regimen has been made exclusionary
- Specific current ALT and hematologic abnormalities have been made exclusionary. The criterion of obtaining a specimen for these lab tests at birth has been removed.
- Required concomitant use of rifampin or oral ketoconazole has been made exclusionary.

Note at the end of the section, The window for randomization and re-assessment of lab abnormalities prior to randomization has been specified.

Note at the end of the section, instructions that the 6-week evaluations are not required for randomization has been added. And that the conditions noted in the randomization criterion are exclusionary if known prior to randomizing/dosing.

Last paragraph, the randomization procedures in the case of multiple births has been inserted from Section 4.3

- Section 5.1 has been modified as follows:

Section 5.1.1, the window for maternal eligibility evaluations has been updated

Section 5.1.1, the tests acceptable for confirmatory HIV testing have been updated

Section 5.1.1, dried blood storage has been added

Note after section 5.1.1, the reference for the Specimen Storage Consent has been updated to Appendix II C

Section 5.1.2, the window for maternal labor and delivery evaluations has been updated

Section 5.1.2, dried blood spot storage has been added

Section 5.1.3, the follow-up schedule for mothers of infants not randomized has been specified

Section 5.1.3, confirmation of intent to breastfeeding has been added to the 6-week visit clinical evaluations

Section 5.1.3, dried blood spot storage has been added to laboratory evaluations

- Section 5.2 has been modified as follows:

Section 5.2.1, the window for infant evaluations prior to enrollment has been updated

Section 5.2.1, cell pellet storage has been added

Section 5.2.1, dried blood spot storage has been added

Section 5.2.2, the note with the follow-up schedule for randomized infants has been modified to include instructions for follow-up of randomized infants in Version 2.0 and enrolled and not randomized infants in Version 2.0 and 3.0.

Section 5.2.2, the clinical evaluations scheduled for 4 weeks have been re-scheduled for 5 weeks.

Section 5.2.2, the laboratory evaluations scheduled for 4 weeks have been re-scheduled for 5 weeks and CBC was added at 5 weeks

Section 5.2.2, confirmation of mother's intent to breastfeeding has been added to the 6-week visit evaluations

Section 5.2.2, plasma storage has been added to the 5 and 8 week laboratory evaluations

Section 5.2.2, cell pellet storage has been added

Section 5.2.2, dried blood storage has been added

Note at the end of the section, instructions for follow-up of infants that have an initial positive HIV test and the schedule for follow-up of infants that are receiving open-label NVP and determined to be HIV infected have been added

- Second to last paragraph of Section 5.2, the follow-up schedules for infants that have NVP permanently discontinued prior to randomization and their mothers have been specified.

Last paragraph, the follow-up schedule for randomized infants that have study drug permanently discontinued has been clarified.

- Section 5.3 has been modified as follows:

Paragraph 1, the evaluations for mothers in the case of early withdrawal have been clarified in that the procedures are for mothers of randomized infants

Last bullet, dried blood spot storage has been added.

- Section 5.4 has been modified as follows:

Line 1 of paragraphs 1 and 2, the evaluations for infants in the case of treatment discontinuation or study withdrawal have been clarified in that the procedures are for randomized infants.

Bullets under paragraph 1 and 2, cell pellet and dried blood spot storage have been added

- Section 5.5, the follow-up schedule for enrolled infants that are not randomized has been specified.

- Section 5.7 has been modified as follows:

Paragraph 1, receipt of open label NVP has been added to the toxicity management procedures. The toxicity management procedures are unchanged from the toxicity management procedures in Version 2.0. for study drug.

Last paragraph, the follow-up schedule for mothers of infants that have been randomized has been added.

- Section 5.9, guidelines for participant co-enrollment in other clinical trials have been added.

- Section 6.1, the treatment formulation and content for the open-label NVP regimen has been specified.

- Section 6.2 has been modified as follows

Paragraph 1, the open-label NVP regimen has been specified; the study drug regimen has been updated

Paragraph 2, the maximum amount of oral NVP or study drug and syringes that may be dispensed at one time has been specified. A condition that mothers who are not available for a visit during the next study window will not receive any study product until they again return to the clinic has been specified.

Paragraphs 3, procedures for the administration of the open-label NVP regimen have been specified.

Paragraph 3, the duration of follow-up for not-randomized infants determined to be HIV-infected has been specified and the duration of follow-up for randomized infants has been clarified.

Paragraph 4, the treatment regimen (open-label NVP and study product) for infants enrolled in Version 3.0 of the protocol and infants randomized in Version 3.0 of the protocol has been specified. The treatment regimen for infants enrolled in Version 2.0 of the protocol who were randomized to the placebo arm and over 6 weeks of age as of 10 Aug 2007 or randomized to the nevirapine arm has been specified. The treatment regimen for infants enrolled on or after 10 Aug 2007 in Version 2.0 of the protocol or who were either randomized to the placebo arm and under 6 weeks of age as of 10 Aug 2007 has been specified.

The Infant Dosing Regimen Table has been modified as follows,

- The regimen for open-label NVP has been added
- The dose adjustment at 4 weeks has been changed to 5 weeks
- The study drug regimen has been updated

A note which clarifies the definition of infant age and provides guidance for the time points at which infants can receive a dose adjustment has been added.

A note which includes the dosing regimen for infants enrolled in Version 2.0 has been added

Section 6.2.1, paragraph 1, open-label NVP regimen has been specified. The criteria for initiating and instructions for dosing open-label NVP in infants that have been enrolled has been specified. These initial dosing criteria are unchanged from the initial study drug dosing criteria in Version 2.0 of the protocol except it has been specified that infant must have been exposed to breastmilk in the last 30 days.

Section 6.2.1, the conditions for exclusion of initial dosing of open-label NVP are unchanged from conditions for exclusion of initial dosing of study drug in Version 2.0 of the protocol except where noted below. The procedures specified in this section are for open-label NVP which replaces study drug in the entire Section.

Section 6.2.1, the procedure for contacting the mother if laboratory results from samples obtained at birth are exclusionary has been removed. (The window for enrollment has been widened, so these results are required prior to enrollment and are specified in the enrollment criteria in Section 4.2.)

Section 6.2.1 Inclusion Criterion, (the initial DNA PCR result from birth specimen criterion as noted above has been moved to Section 4.2.) The criterion for DNA PCR testing has been modified so that a negative result from a specimen obtained at the current visit or within the previous three weeks is required before initiation of open-label NVP.

Section 6.2.1 Exclusion Criteria, (the results of the ALT, Hgb, absolute neutrophil count and platelet count from the birth specimen as noted above have been moved to Section 4.2.) The criteria related to abnormal ALT, Hgb, absolute neutrophil count and platelet count results have been modified so that these conditions are exclusionary if they are current.

Note at the end of Section 6.2.1, has been modified to indicate that enrolled infants that do not initiate the open-label NVP regimen are not eligible for randomization.

Section 6.2.2, the conditions for exclusion of subsequent dosing of open-label NVP are unchanged from conditions for exclusion of subsequent dosing of study drug in Version 2.0 of the protocol. The procedures specified in this section are for open-label NVP which replaces study drug in the entire Section.

Note 1 at the end of Section 6.2.2, the timeframe for obtaining a negative HIV-1 DNA PCR test prior to resumption of open-label NVP when there has been a gap in dosing after initiation has been updated and it has been specified that the infant must have been exposed to breastmilk in the last 30 days before open-label NVP can be resumed.

Note 2 at the end of Section 6.2.2, instructions to consult the Protocol Safety Review Team (PSRT) with any concerns or questions about the resumption of open-label NVP dosing has been added.

Note 3 at the end of Section 6.2.2, the follow-up schedules for enrolled infants and their mothers who have open-label NVP permanently discontinued have been specified.

Note 4 at the end of Section 6.2.2, instructions to permanently discontinue open-label NVP for infants determined to be HIV infected and the follow-up schedules for these infants and their mothers have been specified.

Section 6.2.3, the procedures for initial and subsequent study drug dosing following randomization are unchanged from conditions for exclusion of subsequent dosing of study drug in Version 2.0 except where noted below:

Paragraph 1, the timeframe and procedures for initial study drug dosing have been updated.

Paragraph 2, the conditions for exclusion from doses of study drug after randomization has been updated to include procedures for both initial and subsequent doses

Note 1 at the end of Section 6.2.3, the timeframe for obtaining a negative HIV-1 DNA PCR test prior to initiation of study drug or resumption of study drug when there has been a gap in dosing after initiation has been updated and it has been specified that the infant must have been exposed to breastmilk in the last 30 days before study drug can be resumed.

Note 2 at the end of Section 6.2.3, instructions to consult the Protocol Safety Review Team (PSRT) with any concerns or questions about the resumption of open-label NVP dosing has been added.

A note with and instructions to consult the Protocol Safety Review Team (PSRT) with any concerns or questions about the initiation or resumption of study drug dosing has been added.

Last paragraph, the follow-up schedule for infants and their mothers who never initiate or permanently discontinue study drug has been specified.

- Section 7.0, the following has been modified

Paragraph 1, last sentence, it is clarified that normal variations in typical neonatal conditions that are not regarded as unfavorable are not considered reportable adverse events has been specified.

Paragraph 6, the EAE reporting period has been updated from study enrollment until study completion or until the infant is discontinued for any reason.

Paragraph 7, the AE reporting timeframe and the procedure for monitoring AE events until resolution for infants that receive only open-label NVP have been specified.

Paragraph 10, open-label NVP has been added as a drug that will be considered when determining the relationship to AEs. The open-label NVP regimen has been specified.

Paragraph 10, the study drug regimen has been updated.

- Section 8.0 has been modified as follows:

Section 8.1, the study design has been updated

Section 8.2.1 primary endpoints, the first primary objective has been updated

Section 8.3.1, paragraphs 1, 2 and 3, the power calculations for the primary efficacy outcome have been updated

Section 8.3.1, paragraph 3, the target number of mother/infant pairs for enrollment has been updated

Section 8.3.1, last paragraph, the target number of mother/infant pairs for randomization has been updated.

Section 8.3.2, the power calculations for safety monitoring have been updated

Section 8.4, paragraph 1, the window for enrollment and timeframe for randomization have been updated

Section 8.4 last paragraph the stratification for randomization procedures have been updated

Section 8.6.1, paragraph 1, the definition of HIV infection at the time of randomization has been updated

Section 8.6.2, an analysis plan for the cohort of infants enrolled in Version 2.0 of the protocol has been added.

- Section 9.0 has been modified as follows:

Section 9.2, paragraph 1, a reference to an additional consent form for infants enrolled in Version 2.0 has been added.

Section 9.3 last paragraph, additional information on access to HIV-related care at each site and plans for referring and facilitating treatment for HIV infected infants has been specified.

Section 9.4, the provision for including the amount of compensation in the consent form has been updated

- Section 10.0 has been modified as follows:

Section 10.2 list of bullets, dried blood and cell pellet storage have been added
Section 10.3 paragraph 2, the percentage of quality assurance retesting of enrolled women for the presence HIV antibody to confirm HIV-1 infection was updated to 10%.

Appendix 1A, Schedule of Maternal Evaluations, has been modified as follows:

The window for screening and enrollment has been updated
Confirmation of intent to breastfeed has been added to the 6 week procedures
Dried Blood Spot storage has been added
Note at the bottom of the table, the follow-up schedule for mothers of infants enrolled and not randomized in Version 2.0 of the protocol has been specified.
Note at the bottom of the table, the follow-up schedule for mothers of infants enrolled and not randomized in Version 3.0 of the protocol has been updated

Appendix 1B, Schedule of Infant Evaluations, has been modified as follows:

The window for enrollment has been updated
Confirmation of mothers' intent to breastfeed has been added to the 6 week procedures
The 4 week visit changed to 5 weeks
CBC has been added at 5 weeks
Real-time Roche Amplicor HIV-1 DNA PCR testing has been moved from 6 weeks to 5 weeks
Plasma storage has been added at 5 weeks and 8 weeks
Dried Blood Spot storage has been added at Enrollment, 2, 5,6 and 8 weeks and 3, 6, 9, 12 and 18 months
Cell Pellet Storage has been added at Enrollment, 2, 5,6 and 8 weeks and 3, 6, 9, and 12 months
Note at the bottom of table, the follow-up schedule for infants enrolled and not randomized in Version 2.0 of the protocol has been specified
Note at the bottom of the table, the follow-up schedule for infants enrolled and nor randomized in Version 3.0 of the protocol has been specified
Note at the bottom of the table, the schedule of evaluations at 4 weeks for infants enrolled in Version 2.0 of the protocol has been specified.

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

The consent form has been updated to reflect the design changes described above in the following sections where relevant:

Purpose of the Study
Procedures
Mothers Procedures
Baby's Procedures
Weaning
Risks and/or Discomforts
Potential Benefits

Statement of Consent, the participant and witness affidavits have been updated to first person language

To simplify the language, minor wording changes were made; “syrup” was replaced by “liquid,” and “eligible” was replaced by “able to participate.”

Appendix II B, Sample Study Consent Form for Subjects Enrolled Under Version 2.0 To Continue in the Study Under Version 3.0 has been added. This consent form is generally consistent with the original consent form in Appendix II A. The layout is slightly different to allow for specifications of follow-up for the different sub-groups.

Appendix III, Supplemental Table For Grading The Severity of Cutaneous/Skin Rash/ Dermatitis, Malnutrition and Fever has been modified as follows:

Under Diffuse erythematous macular or maculopapular cutaneous eruption or moist desquamation with or without pruritis together and the constitutional findings considered related to study drug fever has been modified from $> 39^{\circ}C$ to Grade 2

Appendix IV, Toxicity Management Procedures, have been modified as follows

Statement before the table, enrolled infants that are receiving open-label NVP have been added to the management procedures.

Table, instructions for the management of incidences of neutropenia and anemia have been added.

Appendix V, HPTN 046 Adverse Event Reporting and Documentation Requirements, the 2nd column header, open-label NVP has been added.

Appendix A : Modifications to the Introduction and Background - Section 1.0

Deletions in the protocol text are indicated by strikethrough and additions are indicated in **bold**.

Section 1.0 Introduction and Background

Paragraph 1 has been modified as follows:

In ~~2002~~ **2006**, an estimated ~~800,000~~ **530,000** children became infected with HIV, mainly in developing countries. Since the beginning of the HIV epidemic, an estimated ~~5.4~~ **2.3** million children worldwide have been infected with HIV.

Paragraph 2, the last sentence has been modified as follows:

It is, therefore, the goal of this study to evaluate an intervention that may enable HIV-infected mothers who wish to breastfeed **for an extended period**, or who have no other option, to do so while still protecting their infants from HIV infection.

Paragraph 3 and 4 have been added as follows:

The amendment from Version 2.0 of this protocol to Version 3.0 was precipitated by a recommendation by the NIAID Data and Safety Monitoring Board overseeing the study that the placebo control be replaced with a regimen of open-label nevirapine given to infants through 6 weeks (42 days) of life. This recommendation was based on preliminary results of a pre-planned combined analysis of three other studies (collectively known as the Six Week Extended Nevirapine (SWEN) study) which showed that 6 weeks of NVP to breastfeeding infants in India, Uganda and Ethiopia significantly reduced the risk of HIV transmission from mother to infant at 6 weeks of age and was associated with significantly lower mortality rates at 6 months and 6 weeks of age. Additional details about the SWEN study are provided below.

While data from the SWEN study indicate that a short 6 week infant nevirapine (NVP) regimen reduces the risk of early postnatal transmission and increases HIV-free survival in India, Uganda and Ethiopia continued breastfeeding for more than the first few months of life may negate this early efficacy result. Other data are accumulating that early weaning prior to age 6 months may be associated with excess infant morbidity and mortality among uninfected infants. Based on these data, the World Health Organization recently changed their infant feeding guidelines for infants of HIV-infected women to recommend 6 months of exclusive breastfeeding if replacement feeding is not acceptable, feasible, affordable, sustainable and safe (AFASS); if at 6 months, replacement feeding is still not AFASS, continued breastfeeding with additional complementary foods is recommended while mother and infant continue to be regularly assessed regarding AFASS criteria (11). Given the need for more extended breastfeeding in many resource-limited countries, whether extending NVP prophylaxis through age 6 months would be safe, offer significant additional efficacy, and be cost-effective in prevention of postnatal transmission is unknown and important to address.

The last paragraph has been modified as follows:

In HPTN 046, all infants will receive NVP up to 6 weeks (42 days) of age, and those eligible will be randomized at age 6 weeks to either continue NVP or NVP placebo from age 6 weeks through age 6 months ~~This Phase III trial will evaluate the efficacy and safety of a daily regimen of nevirapine (NVP) provided to infants for 6 months or through the cessation of breastfeeding~~

(whichever is earliest). **The trial will evaluate the efficacy and safety of an extended regimen of NVP suspension from 6 weeks through 6 months of age or until cessation of breastfeeding compared to placebo for prevention of MTCT in breastfeeding infants who are born to HIV-infected women and provided open-label NVP for the first six weeks of life.** As standard of care (external to the study) all HIV-infected women at the study sites are offered **at minimum** the HIVNET 012 two-dose intrapartum/neonatal regimen of NVP. The daily regimen of NVP was chosen for this study based on the safety and pharmacokinetic data from HIVNET 023 in which daily, weekly, and twice weekly dosing regimens were compared (see Section 1.5). A placebo controlled study design will be used because there are currently no conclusive data on potential efficacy of **extended** postpartum interventions **to significantly further** diminish transmission when the infant is breastfed **and had received 6 weeks of NVP prophylaxis.** There may also be side effects of **prolonged administration of** administering drug to healthy infants; therefore it is essential to ascertain that the benefit is greater than any risks incurred. A primary objective of the study is to evaluate and compare the safety and tolerance in the two arms. The placebo-controlled design allows for the most accurate and appropriate assessment of both efficacy and safety.

Section 1.1.3 has been modified as follows:

Section 1.1.3 ~~Preliminary SIMBA and Mashi Study Results~~ **Data from Infant Prophylaxis Trials**

Paragraphs 1 and 2 have been added as follows:

Data from Three-Country Trial of Six-Week NVP Suspension Prophylaxis of Postnatal Transmission

A recent preliminary pre-planned combined analysis of data from three clinical trials in Ethiopia, India and Uganda (the SWEN Study) evaluating NVP suspension in the first 6 weeks of life plus multivitamins compared to standard single-dose intrapartum/neonatal NVP plus multivitamins for prevention of HIV transmission through breastfeeding have become available. The study included 1,920 live-born infants. In this study, all mother-infant pairs received single-dose intrapartum/neonatal NVP for prevention of intrapartum transmission, and were randomized to 6 weeks (42 days) of NVP versus only the standard single-dose NVP regimen. Among infants who were HIV DNA PCR negative or RNA PCR negative at birth, the infection rate at age 6 weeks was 2.6% in the 6-week NVP group vs. 5.1% in the single-dose NVP group (unadjusted relative risk 0.539, p=0.0003) and at 6 months, the HIV infection rate was 6.7% vs. 8.3%, respectively (unadjusted relative risk 0.789, p=0.066). There were significant decreases in mortality that persisted to 6 months, with a 60% reduction in the risk of death at age 6 months in the 6-week NVP arm (mortality in the 6-week NVP group 1.8% vs. 3.7% in the single-dose NVP group, unadjusted relative risk 0.403, p=0.00008); the 6 month rate of HIV infection or death was 8.3% in 6-week NVP group compared to 11.5% in the single-dose NVP group (unadjusted relative risk 0.708, p=0.002). While there were significant differences in efficacy across the sites that are currently being thoroughly examined, the overall conclusion about the efficacy of the 6-week NVP regimen in preventing HIV transmission during breastfeeding will not be altered. Analyses including important covariates such as duration of breastfeeding and maternal CD4 and RNA are underway but not yet available. Analysis of adverse event data are ongoing; however, multiple past reviews of safety data by the independent Data and Safety Monitoring Board (DSMB) did not identify any concerns regarding the safety of the 6-week NVP regimen.

Given the significant difference in HIV-free survival in the SWEN study with 6 weeks of NVP prophylaxis, HPTN 046 is modified from its original design of 6 months of NVP suspension compared to NVP placebo for prevention of postnatal transmission, to a study design in which all infants receive 6 weeks of open-label NVP and then receive either NVP or NVP placebo from age 6 weeks to age 6 months or cessation of breastfeeding (whichever comes first). It is important to continue to evaluate the 6 month NVP prophylaxis course for several reasons: 1) there was some evidence that the effect of the 6-week NVP regimen on HIV transmission was greatest at age 6 weeks, with diminution at 6 months with continued breastfeeding; 2) the 6 month postnatal transmission rate of 6.7% in the 6-week NVP arm is still relatively high; 3) preliminary uncontrolled data from two trials, SIMBA and MITRA, suggest that 6 month postnatal transmission rates as low as 2% can be achieved with a 6 month regimen; and 4) recent data suggesting that early weaning is not advisable in many resource-limited countries, with WHO recommendations now calling for 6 months of exclusive breastfeeding if AFASS criteria are not met.

Preliminary SIMBA, MITRA and Mashi Study Results of 6-Month Infant Antiretroviral Prophylaxis

Paragraph 1, SIMBA was a randomized, open-label study sponsored by the International Antiviral Therapy Evaluation Center (IATEC) conducted in Uganda and Rwanda in which 405 women received dual antiretroviral therapy with ~~zidovudine (ZDV)~~ **azidothymidine (AZT)** and didanosine (ddI) from 36 weeks of pregnancy, intrapartum, and for 1 week postpartum.

Paragraph 2, next to the last sentence, While these women still had median HIV RNA (3.8 log) that was more than 1 log higher than the median level in SIMBA, these two groups likely had similar median viral loads before receiving ~~antivirals~~ **antiretrovirals**, (assuming AZT/ddI leads to a 1.1 decrease in log HIV RNA).

The following paragraph has been added:

The MITRA Study was conducted in Tanzania and had similar problems with interpretation as did the SIMBA study. MITRA also had an antepartum-intrapartum-postpartum regimen in addition to an infant prophylaxis component; it evaluated the PETRA AZT + lamivudine maternal/infant regimen (starting at 36 weeks gestation, given orally, during labor and for one week postpartum to mother and infant), and breastfeeding infants then continued 3TC alone for 6 months. They reported an overall transmission rate at 6 weeks of 3.4% (95% CI, 1.6-5.2%) and at 26 weeks of 5.1% (95% CI, 2.9-7.3%), with an incremental postnatal transmission between 6 and 26 weeks of 1.7% (33). The median duration of breastfeeding was 20 weeks, with only 23% still breastfeeding at 26 weeks. The SIMBA or MITRA studies, while presented in abstract form, have not been published.

Data are also available ~~More recently, data have been presented~~ from the Mashi Study, conducted in Botswana (34). This study was a factorial design in which mother-infant pairs were randomized by feeding strategy and then randomized again by whether they receive the single-dose mother/infant regimen of NVP or placebo. In this study, all HIV-infected women received AZT starting at 34 weeks gestation and orally intrapartum, and all infants received one month of AZT; infants were randomized to formula feed (with one month of AZT) or to breastfeed with ~~six-6~~

months of infant AZT prophylaxis. The median duration of breastfeeding was 5.8 months, almost three months longer than in the SIMBA study.

Despite the infant AZT prophylaxis during the breastfeeding period, at age seven months, HIV transmission was significantly higher in the breastfed + AZT arm than the formula-fed arm (overall transmission at age seven months 5.6% transmission with formula vs 9.1% with breastfeeding + AZT). **The incremental rate of postnatal transmission in the breastfeeding + AZT arm occurring between age 1 month (4.6%) and 7 months (9.1%) was 4.5%.** Infant mortality was significantly higher in the formula-fed than breastfed infants at age seven months (9.3% mortality with formula vs. 4.9% with breastfeeding + AZT), but became similar by age 12 months (10.9% formula vs. 9.5% breastfed + AZT). By age 18 months, HIV-free survival was similar between the formula and breastfed + AZT group; however this is because in the formula fed group, while there was less transmission (33 infants infected) than in the breastfed + AZT group (54 infants infected), the mortality in the formula fed group (46 deaths) was higher than in the breastfed + AZT group (34 deaths).

~~The overall transmission rates were similar in the SIMBA (8%) and Mashhi (9%) studies. Like SIMBA, the lack of a control group (e.g., a group of infants breastfeeding without 6 month infant AZT prophylaxis) in the Mashhi study makes the data inadequate to accurately assess the potential efficacy of 6 month infant prophylaxis of postnatal transmission. However, in the Mashhi study, the fact that the infection rate at age seven months in the breastfeeding group, in which six months of infant AZT prophylaxis was given, was significantly higher than in the formula feeding arm is of concern. Additionally, the Mashhi data suggest the importance of identifying ways to safely breastfeed, given the higher infant mortality with formula feeding.~~

~~Therefore, there remains a critical need for a randomized, placebo-controlled trial to determine the efficacy and safety of infant prophylaxis in reducing breast milk HIV transmission. Inclusion of a placebo control is essential for accurately evaluating the safety of six months of daily NVP. Given the concerns with potential drug-related toxicities—specifically rash, liver abnormalities, and neutropenia—and lack of existing data on the background rates of these in the study population, it is critical to have an untreated placebo arm to assess true relatedness of observed events to study product. Subjective determination of relatedness based only on individual investigator determination at the time of event assessment has the potential to either overestimate or underestimate true drug related toxicity and thus would not provide sufficient information to accurately evaluate the risk:benefit ratio. Currently, there is no proven alternative ARV regimen for prevention of MTCT through breastfeeding that is feasible in resource limited settings, and as shown above, with The SIMBA and MITRA studies any design other than the most rigorous and appropriate (randomized, placebo-controlled), will not do provide preliminary data to support the hypothesis that more extended infant postnatal prophylaxis could provide significant benefit in further reducing postnatal transmission. In the SWEN study, the 6-month transmission rate in infants uninfected at birth who received the 6-week NVP regimen was 6.7%; in the SIMBA study, the infection rate in infants uninfected at birth who received one of the 6-month regimens was 1.6%. Also, in the SWEN study, the increment in postnatal infections between 6 weeks and 6 months in infants uninfected at 6 weeks in the treatment group was 4.1%, whereas in the MITRA study, the incremental postnatal transmission rate during a similar period was 1.7%.~~

Data on Adverse Effects of Early Infant Weaning (Prior to 6 Months)

At an October 2006 WHO meeting on infant feeding by HIV-infected mothers, a number of studies were reviewed which led to the WHO modifying their infant feeding guidelines to recommend at least 6 months of exclusive breastfeeding if AFASS criteria are not met (11). In these studies, early cessation of breastfeeding (before 6 months) was associated with an increased risk of infant morbidity (especially diarrhea) and mortality in HIV-exposed children in studies in Malawi, Kenya, Uganda and Zambia.

Data on gastroenteritis and mortality in HIV-exposed but uninfected infants were compared in an ongoing clinical trial (the PEPI trial), in which women are counseled to wean early, to an earlier trial (NVAZ Trial) in the same clinics where women breastfed for over 12 months (35). In the PEPI study, gastroenteritis frequency and hospitalization was highest in uninfected infants between the ages of 7-9 months, immediately following weaning, and gastroenteritis-related mortality was significantly higher in PEPI infants (where there was early weaning) than in NVAZ infants (where there was prolonged breastfeeding with delayed weaning): gastroenteritis-related mortality was 28 per 1,000 infants in PEPI vs. 12 per 1,000 infants in NVAZ at 12 months. Thus, gastroenteritis-related deaths in uninfected infants were more than two-fold higher in the PEPI compared to the NVAZ study.

In Kenya, data from an ongoing study of maternal prophylaxis of breastfeeding transmission (KiBS), where early weaning is recommended, were compared to data from a vertical transmission study (VT) conducted in 1996-2001 where early weaning was not recommended (36). The KiBS infants showed an increased risk of diarrhea and diarrhea-related hospitalizations at 6 months, the period of weaning, compared to the VT study.

In the HIVIGLOB study in Uganda (which had 3 arms, two that were a component of the SWEN study - single-dose NVP vs. 6-week NVP - and a third arm evaluating hyperimmune HIV immunoglobulin for prevention of transmission), mothers were counseled to exclusively breastfeed for 3-6 months and abruptly wean; the median duration of breastfeeding was 3 months (37). The rates of gastroenteritis were compared pre- and post-weaning. Breastfeeding cessation was associated with increased risk of serious gastroenteritis among HIV-uninfected infants, with a doubling in rate post-weaning compared to pre-weaning, and infant deaths rose sharply within 3 months after breastfeeding cessation.

Early breastfeeding cessation at 4 months was not only associated with reduced HIV transmission but also with increased child mortality from 4 to 24 months in the Zambia Exclusive Breastfeeding Study (ZEBS) randomized trial (38). In the ZEBS study, 958 women counseled to exclusively breastfeed for 4 months were randomized to abrupt weaning at 4 months compared to continued breastfeeding (median duration of breastfeeding was 16 months in the latter group). At age 24 months, there was no difference in HIV-free survival between the 2 groups, with a higher than anticipated rate of mortality among uninfected infants in the abrupt weaning group.

These studies suggest that in many resource-limited countries, exclusive breastfeeding until at least 6 months of age would be more beneficial to the infant than early weaning despite the continued risk of HIV transmission posed by continued breastfeeding.

Conclusions:

Given the results of the SWEN study, all infants enrolled in HPTN 046 who are, by definition, breastfeeding, should receive the 6 week NVP prophylaxis regimen. This regimen reduced the risk of postnatal transmission in infants uninfected at birth to 6.7% at age 6 months in the SWEN study.

However, it is clear that in many resource-limited countries, more prolonged breastfeeding through at least 6 months of age remains critical to reduce infant morbidity and mortality. Therefore, should the 6-week infant prophylaxis be implemented on a wide scale there would still be a continued risk of HIV transmission for infants after the 6 week NVP prophylaxis period has been completed. Interventions are needed to reduce that risk and the concomitant HIV-associated mortality. Uncontrolled data from the SIMBA and MITRA studies suggest that 6 months of infant antiretroviral prophylaxis may significantly further reduce postnatal transmission.

There are major issues raised regarding use of 6 months rather than 6 weeks of infant antiretroviral prophylaxis. The cost of daily prophylaxis for 6 months is significantly higher than for 6 weeks. The safety of extended antiretroviral drug administration to otherwise healthy infant is unknown. From a programmatic point of view, it is much more complex to initiate programs providing 6 months rather than 6 weeks infant prophylaxis, and feasibility is unclear. Thus, rigorous and appropriate (randomized, placebo-controlled) clinical trials to yield conclusive results with practical implications that are informative to policy makers, health care organizations/providers and donors are needed before it can be concluded that 6 months of infant prophylaxis is superior to 6 weeks.

Thus, there remains a critical need for a randomized, placebo-controlled trial to determine the efficacy and safety of extended infant prophylaxis in reducing breast milk HIV transmission. Inclusion of a placebo control is essential for accurately evaluating the safety of six months of daily NVP. Given the concerns with potential drug-related toxicities - specifically rash, liver abnormalities, and neutropenia - and lack of existing data on the background rates of these in the study population, it is critical to have an untreated placebo arm to assess true relatedness of observed events to study product. Subjective determination of relatedness based only on individual investigator determination at the time of event assessment has the potential to either overestimate or underestimate true drug related toxicity and thus would not provide sufficient information to accurately evaluate the risk-benefit ratio.

Section 1.2 Rationale for Extended Regimen of Infant NVP to Prevent MTCT, has been modified as follows:

Paragraph 1, last sentence

To that end, this study proposes to test the efficacy of providing an extended prophylactic antiretroviral regimen to breastfeeding infants born to HIV-infected women **from over a maximum period of 6 weeks to 6 months of life (or through cessation of breastfeeding)** for prevention of MTCT through breast milk **compared to placebo among infants provided a 6 week prophylaxis regimen**. ~~Because the maximal benefit from breastfeeding is during the first 6 months of life, there is continued risk of HIV transmission for the duration of breastfeeding, so weaning by age 6 months will be encouraged (34). Others have similarly shown that the protective effects of breastfeeding are greatest in the first 6 months of life (17,18).~~

Section 1.6 Rationale for Infant Daily Dosing Regimen

The table has been modified as follows and the paragraph below has been to the end of this section

Age	Dose (mg)	NVP: mg/kg		
		Average weight infants NVP mg/kg	Lowest weight infant NVP mg/kg	Heaviest infant NVP mg/kg
All infants will receive NVP from 3 to 7 days after birth through age 6 weeks (42 days of age)				
Birth	6	2.01	3.00	1.33
1 week	6	1.83	3.75	1.20
2 weeks	6	1.70	2.40	1.30
	15	4.26	6.00	3.26
Eligible infants will be randomized to receive study drug (NVP or NVP placebo) from 43 days of age through 6 months of age.				
6 weeks	15	3.25	6.00	2.27
	18	3.90	7.20	2.73
8 weeks	18	3.45	5.14	2.81
	20	3.84	5.71	3.13
10 weeks	22	4.03	6.88	2.75
12 weeks	No weight data available			
14 weeks	24	3.93	7.50	2.58
16 weeks	24	3.59	4.80	2.82
	26	3.89	5.20	3.06
20 weeks	26	3.57	5.31	2.95
	28	3.85	5.71	3.18
24 weeks	28	3.66	5.19	2.95

The SWEN study used a smaller dose of study drug (NVP or placebo) (0.5 ml [5 mg] once daily), starting at approximately age 7 days and continuing through 42 days (6 weeks) after birth. However, the dosing chosen for HPTN 046 was derived from pharmacokinetic and safety data from HIVNET 023 and based on maintaining the minimum concentration of 100 ng/ml target, as explained above. Additionally, as of 4 August 2007, 282 infants have been randomized in HPTN 046 and have received dosing as per section 6.2, beginning at age 5 days (\pm 2 days). Therefore, HPTN 046 will continue to use NVP dosing during the first 6 weeks of life that is consistent with the dosing that has been used in the HPTN 046 study to date.