

**SUMMARY OF CHANGES  
INCLUDED IN THE  
FULL PROTOCOL AMENDMENT 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 1.0, DATED 10 OCTOBER 2003**

**THE AMENDED PROTOCOL IS IDENTIFIED AS  
FINAL VERSION 2.0 AND DATED 22 May 2005**

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**Summary of Revisions and Rationale**

The modifications included in this protocol amendment and the rationale are summarized briefly below and detailed in the 'implementation' section that follows. The modifications are presented generally in order of their first appearance in the study protocol.

With this amendment, the modifications included in Letter of Amendment #1 to Version 1.0, dated 6 July 2004, and the additional information included in Clarification #1 to Version 1.0, dated 7 April 2004, are formally incorporated into the protocol document.

HPTN 046 study investigators will submit this Summary of Changes and the corresponding protocol Version 2.0 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 2.0 of the protocol may be implemented.

1. The protocol has been updated throughout to reflect the sponsor's decision to conduct the trial under an Investigational New Drug (IND) application with the US Food and Drug Administration.
2. The protocol title page and team roster have been updated to reflect changes in contact information and personnel.
3. The background (Section 1.1.3) has been updated to include recently released results of the Mashii study in Botswana as well as additional rationale for use of a placebo control. Section 1.4.1 (Pharmacokinetics of NVP Treatment in HIV-infected Infants and Children) has been revised to clarify the rationale for the dosage of NVP to be used in the study. Section 1.4.3 (Safety of NVP Used for Treatment of HIV Infection) has been updated with additional information about hepatic toxicity from the Viramune® Package Insert and more extended discussion of nevirapine (NVP) use in patients without HIV infection. Section 1.4.4 (Development of NVP Resistance with NVP Used for Treatment Section does not list the common mutations seen as the mutations seen are broader than those specified. 1.6 (Rationale for Infant Daily Dosing Regimen) has also been revised to include additional justification for the chronologic NVP dosing schedule based on age that is being used in the study.
4. References to the standard of care regimen for prevention of mother to child HIV transmission (pMTCT) offered to all mother and infants outside of the study have been broadened from the intrapartum/neonatal regimen of nevirapine (which currently remains the standard of care at the

participating sites) to acknowledge that other ARV regimens may also be used in standard practice for pMTCT in these settings over time.

5. The definition of cessation of breastfeeding has been further clarified to specify completely stopping all exposure to breast milk for 30 days.
6. Procedural specifications for HIV testing in infants 15 months of age or older have been updated to allow for use of rapid HIV testing. In addition, the definition of HIV infection for infants  $\geq 15$  months of age has been clarified to indicate that a Western blot or IFA must be performed on the first sample and again on a sample drawn on a different day to confirm HIV infection. Section 2.3 and procedural specifications for HIV testing in infants less than 15 months of age have been modified to allow for quantitative HIV-1 RNA-PCR to be used if HIV-1 DNA PCR is not available. It is also clarified that confirmatory HIV tests for infants  $< 15$  months of age must also be performed on a specimen drawn on a different day than the original sample.
7. The protocol has been modified to include routine infant ALT testing at 4 and 8 weeks (in addition to the previously specified ALT monitoring timepoints at birth, 2 and 6 weeks). This results in routine ALT monitoring every two weeks for the first two months of life. (ALT testing will also be performed if an infant presents with an unexplained rash or unexplained Grade 3 or 4 event other than hepatic toxicity or rash.)
8. The maternal eligibility criteria have been simplified to indicate more clearly that women must be healthy enough to breastfeed and adhere to the follow-up schedule. This clarification results in no effective change in the original eligibility criteria.
9. The maternal study procedures have been modified to indicate more clearly that women screened prior to labor and delivery will have clinical and laboratory assessments repeated at labor and delivery before 3 days post-partum. This clarification results in no effective change in the original assessments.
10. The infant randomization exclusion criterion “Not able to breastfeed” has been switched to the inclusion criterion “Able to breastfeed” to avoid any potential confusion. This clarification results in no effective change in the original eligibility criteria.
11. The descriptive definition of clinical hepatitis included in Section 4.2 and in a footnote to Appendix IV, has been simplified to avoid reference to conditions that are extremely difficult to precisely diagnose in infants; however, there is no effective change in the original definition or its application.
12. Version 1.0 of the protocol states that in the case of multiple births, infants will be included in the study only if both/all are eligible and will be randomized to the same study arm but does not address the case in which only one infant of a multiple birth survives. Therefore, the infant randomization criterion regarding multiple births is clarified to indicate that if only one infant of a multiple birth is alive, that infant could be enrolled if he/she otherwise meets all of the criteria.
13. To eliminate an internal inconsistency between the procedures section of the protocol and the table of evaluations in Appendix IA, the testing requirements for mothers in the case of early withdrawal specified in Section 5.3 of the protocol are corrected to indicate that mothers will be asked to provide a specimen for HIV RNA PCR and NVP resistance testing only rather than for NVP concentration.

14. To simplify data collection procedures and data analysis, the timeframe for reporting infant concomitant medications on case report forms for entry into the study database has been clarified so that it is consistent for all participants, regardless of dosing duration, and consistent with the AE reporting requirements. Infant concomitant medications will be reported through eight months of life rather than through eight weeks post dosing.
15. The protocol has been modified to allow for re-dosing of infants who vomit within 60 minutes of dosing. This is consistent with the manufacturer's recommendation and standard clinical practice.
16. Version 1.0 of the protocol states that mothers will be instructed to begin administration of the study drug to the infant five days after birth ( $\pm$  two days). To further clarify the original intent, procedures to be followed when study drug is not begun within the target timeframe and when there are gaps in dosing have been specified.
17. The title of the recently released DAIDS toxicity table used for grading the severity of adverse events has been specified (DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004), replacing references to the previous version.
18. A positive HIV DNA PCR test result has been added to section 6.2.1 as a condition for exclusion from initial study drug dosing if the test result is known prior to initiating dosing with the note that the result is not required prior to randomization or dispensing study drug.
19. As reflected in Letter of Amendment #1 to Version 1.0, the new 'Manual for Expedited Reporting of Adverse Events to DAIDS' will be employed in HPTN 046. Specifically, the 'standard' level of reporting defined in the Manual will be applied. In addition, the sponsor requested a protocol-specific requirement that all grade 3 and 4 skin rashes and alanine aminotransferase (ALT) levels that otherwise do not meet the criteria for reporting as specified in the Manual also be reported in an expedited manner to DAIDS. A table summarizing the AE reporting requirements has been added as Appendix V.
20. The Confidentiality Section has been corrected to indicate that participant identifiers will be used according to the DAIDS SOPs for Source Documentation and Essential Documents. Specifically, study records bearing participant names are not required to be stored separately from those with participant identification numbers.
21. The protocol has been modified to reflect that plasma HIV-1 RNA viral load assays may be performed at either the HPTN Central Laboratory (CL) at Johns Hopkins University or at qualified site laboratories.
22. The website address where the Study Specific Procedures (SSP) Manual can be accessed has been added.
23. The sample enrollment consent form has been modified to further clarify that the IRB/EC will determine if the father's written consent is required for enrollment, that the relationship between hepatotoxicity and nevirapine dose level is not known, that mothers will have a physical exam soon after birth, that infants will be tested for HIV a total of about 8 times, that ARV treatment for HIV will not be provided through the study, that some blood will be stored for HIV-related study tests and when test results will be given to participants.

24. Severity grading scales for malnutrition and axillary measured fever have been added to Appendix III, now titled Supplemental Table for Grading for Severity of Cutaneous/Skin Rash/Dermatitis, Malnutrition and Fever (Appendix III) as these are not included in the new DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events.
25. The Toxicity Management Procedures in Appendix IV of the protocol have been amended to allow for study drug dosing to be resumed after being held due to occurrence of toxicity in certain circumstances and with concurrence of the Protocol Safety Review Team, if the adverse event has decreased in severity as specified and/or is determined to be due definitively to an alternative diagnosis and not related to the study drug.
26. A table summarizing the adverse event reporting and documentation requirements has been added as Appendix V.
27. Minor wording changes and modifications, such as updating the list of abbreviations and acronyms, have been incorporated throughout.

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### Implementation of Modifications

The following changes have been incorporated into the text of Version 1.5 of HPTN 046 (Draft of Version 2.0, dated 31 March 2005). Deletions in the protocol text are indicated by strikethrough and additions are indicated in **bold**.

#### 1. **IND Status:**

- The IND number has been added to the front of the protocol. References to the US FDA have been added where appropriate in the following sections to indicate information/data to be provided or accessible to the agency and to reflect its regulatory authority:
  - 7.0 Safety Monitoring and Adverse Event Reporting
  - 7.1 Severity Grading
  - 9.5 Confidentiality
  - 9.6 Study DiscontinuationAppendix IIA, Sample Study Enrollment Informed Consent Form (sections entitled ‘Reasons why you or your baby may be withdrawn from the study without your consent’ and ‘Confidentiality’).
- *Section 11.5 Investigator’s Records:* The Investigator will maintain and store in a secure manner complete, accurate, and current study records throughout the study. The Investigator will retain all study records for at least ~~three years after submission of the site’s final Financial Status Report to DAIDS, which is due within 90 days after the end of the site’s cooperative agreement with DAIDS, unless otherwise specified by DAIDS or the HPTN CORE.~~ **two years following the date of marketing approval for the study product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the FDA is notified that the IND is discontinued.**

#### 2. **Personnel:**

The protocol title page and team roster have updated to reflect the following:

- Sheryl Zwierski, RN, MSN, CRNP, replaced Samuel Adeniyi-Jones as the DAIDS Medical Officer.
- Wafaie Fawzie, MD, DrPH, replaced Saidi Kapiga as Protocol Co-Chair representing the Tanzania site.
- Bethany Freeman, MSW, MSPH, has been added as a Protocol Specialist (in addition to Kathy George).
- Contact information for Karim Manji and Lynda Emel has been updated.
- Ying Q. Chen, PhD, has been added as a protocol statistician (in addition to Tom Fleming).
- Melissa Kaufman, MA, has been added as a Protocol Operations Coordinator (in addition to Lynda Emel).
- Sarah Dawson, MS, MT(ASCP)SH has been added as a Central Lab Representative.
- The role for Susan Eshleman has been modified to Protocol Virologist.
- The credentials for Rose Kambarami, MBChB, DCH, FRCP, Mmed SC have been updated.

### 3. Background:

- *Section 1.1.3, Preliminary SIMBA and Mashi Study Results:* Recently released result from the Mashi study in Botswana have been added to this section as well as additional rationale for use of a placebo control. The specific changes are provided in Appendix A of this Summary of Changes.
- *Section 1.4.1, Pharmacokinetics of NVP Treatment in HIV-infected Infants and Children, last sentence:* ~~Because the objective of NVP use in this study is prevention of infection rather than treatment of established infection, reduced doses will be administered.~~ **The NVP dose chosen for the study is based on achievement of a NVP trough level of 100 ng/ml, which was the target level used for determining the NVP dosage in the HIVNET 012 trial in which NVP significantly lowered transmission. Based on data from HIVNET 023 (Section 1.5), this results in administration of NVP doses that are lower than those used for treatment of chronic infection.**
- *Section 1.4.3, Safety of NVP Used for Treatment of HIV Infection:* The paragraph describing skin toxicities was moved to follow the description of liver toxicities; additional information about hepatic toxicity from the Viramune ® Package Insert was added and the discussion of NVP use in patients without HIV infection was extended. The specific modifications in the text are shown in Appendix A of this Summary of Changes. Additional publications are cited in the text added to Section 1.4.3 and have been added to Section 12; these are also provided in Appendix A of this Summary of Changes.

The following reference was deleted from *Section 12*, as it is no longer cited in Section 1.4.3: Centers for Disease Control and Prevention. Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures – worldwide, 1997-2000. MMWR 2001;49:1153-6.

- *Section 1.4.4, Development of NVP Resistance with NVP Used for Treatment.* Second paragraph: ~~The most common mutations seen in clinical isolates of patients treated with NVP are Y181C and K103N.~~ Recent studies have indicated that mutations associated with NVP resistance result in measurable biochemical abnormalities in affected HIV variants ...

- *Section 1.6, Rationale for Infant Daily Dosing Regimen:* Beginning in the fourth paragraph, additional justification for the dosing scheme used in the study has been provided. The modifications in the text are shown in Appendix A of this Summary of Changes.

#### 4. **Standard of Care for PMTCT:**

Specific references to the HIVNET 012 intrapartum/neonatal two-dose regimen of NVP as standard of care for prevention of MTCT at the study sites have been modified in the following sections to refer instead to ‘the local standard of care ARV regimen for prevention of mother to infant HIV transmission’. The HIVNET 012 regimen is noted as an example.

- Schema, Treatment Regimen, ‘Note’ below regimen table
- Section 2.0, Study Design, Paragraphs 2 and 3.
- Section 8.4 Random Assignment and Stratification, Paragraph 2
- Section 6.2, Treatment Dose and Administration, ‘Note’ below regimen table
- Sample Study Enrollment Informed Consent: ‘Purpose of Study’ Section, paragraph 3 and ‘Procedures’ Section, paragraph 2.

#### 5. **Definition of Breastfeeding Cessation:**

- *Section 2.0, Study Design, paragraph 2, sentence 5:* Cessation of breastfeeding is defined as completely stopping all exposure to breast milk **for at least 30 days**.
- *Section 6.2, Treatment Dose and Administration, paragraph 1, sentence 3:* Cessation of breastfeeding is defined as completely stopping all exposure to breast milk **for at least 30 days**.

#### 6. **HIV Testing Procedures:**

- *Section 2.2, Infant Randomization and Follow-Up, paragraph 2, sentence 6:* At 18 months, an HIV EIA ~~or rapid HIV assay test~~ will be performed. **All positive HIV EIA or rapid HIV test results will be confirmed with Western blot or IFA.**

*Paragraph 3, sentences 2 and 3:* Any infant with a positive virologic assay (either positive HIV-1 DNA PCR, ~~or EIA Western blot or IFA~~ at 18 months) will have a repeat assay done on a specimen **drawn on a different day** to confirm infection status. Infants identified as HIV-infected will be taken off of study treatment and remain in follow-up and undergo all scheduled assessments with the exception of adherence and HIV ~~DNA PCR or EIA testing~~.

The following note has been added at the end of the section: **Note: Quantitative HIV-1 RNA PCR may be used if HIV-1 DNA PCR is not available.**

- *Section 2.3, **Diagnostic Testing** Use of Roche Amplicor 1.5 HIV-1 DNA PCR Assay to Determine HIV Infection, paragraph 1, sentence 1:* The DNA test ~~to be used~~ **that is currently available** for diagnosis of infant HIV infection is currently an unlicensed assay in development by Roche Diagnostic Systems.

*Paragraph 2, sentence 3:* Therefore, the HIV-1 Amplicor DNA 1.5 PCR assay **is the preferred test will be used** for diagnosis of HIV infection in infants in this study. **However, Roche Diagnostic Systems may stop manufacturing the 1.5 DNA PCR assay, and use of the standard 1.0 Roche DNA PCR assay would be inappropriate given lack of sensitivity in detection of non-subtype B infection. Therefore, if DNA PCR is not available, quantitative**

**HIV-1 RNA PCR may be used as an alternative for infant diagnosis, as the Roche RNA assay would be appropriate for use in detection of non-subtype B infection.**

- *Sections 4.2, 5.2.1, 5.2.2, 5.4, 6.2.1, 6.2.2, 8.2.1, and 8.3.1* have been modified with the following note: **Note: Quantitative HIV-1 RNA PCR may be used if HIV-1 DNA PCR is not available.**
- *Section 5.2.2, Follow-up Infant Evaluations, Laboratory Evaluations, bullet 5:* HIV EIA or **rapid HIV test** (at 18 months only). If positive, **perform a Western blot or IFA on the first sample and confirm with a different EIA than first test or Western Blot or IFA on a second sample drawn on a different day.** ~~on or before the participant's next scheduled visit.~~
- *Section 8.6.1, Primary Analyses:*

*Definition of in utero HIV infection, last sentence:* However, a second specimen **drawn on a different day** will be obtained and tested, by HIV DNA PCR for confirmation.

*Definition of HIV infection other than through in utero transmission, sentence 2:* Infants older than 15 months of age who are reactive for HIV-1 antibody by ~~two different an~~ **HIV EIA or rapid HIV test or and an HIV-1 Western blot or IFA performed on a second sample drawn on a different day** will be considered to be HIV-1 infected.

- *Section 10.1, Local Laboratory Specimens:* The following tests will be done at the local laboratory (LL): **Rapid HIV test** has been added.
- *Appendix 1B SCHEDULE OF INFANT EVALUATIONS:*

HIV EIA has been changed to HIV EIA or **Rapid HIV Test**.

Footnotes for HIV testing have been modified as follows:

<sup>2</sup> If HIV-1 DNA PCR positive, confirm with a repeat HIV-1 DNA PCR on a second sample **drawn on a different day** ~~obtained on or before the participant's next scheduled visit.~~ **HIV-1 RNA PCR may be used as an alternative if HIV-1 DNA PCR is not available.**

<sup>3</sup> If reactive, **perform a Western Blot or IFA on the first sample and confirm with a different EIA or Western Blot or IFA on a second sample drawn on a different day** ~~obtained on or before the participants next scheduled visit.~~

## 7. ALT Testing:

- *Section 2.2, Infant Randomization and Follow-up, paragraph 2, sentence 3:* Blood samples for the following assays will be drawn at birth, 2, **4**, 6 and **8** weeks and 3, 6 and 12 months: ~~CBC with differential, alanine aminotransferase (ALT)~~ (up to 6 months only), **CBC with differential and HIV-1 DNA PCR (excluding 4 and 8 weeks).**
- An ALT test at 4 and 8 weeks has been added to Section 5.2.2 (Follow-up Infant Evaluations) and Appendix I B, Schedule of Infant Evaluations.

## 8. Maternal Eligibility Criteria:

*Section 4.1, fifth and sixth bullets deleted and replaced by one:*

- ~~No serious current or previous complications of this pregnancy, as judged by the on-site clinician~~
- ~~Free of active serious infection other than HIV or other serious illnesses, as judged by the on-site clinician~~
- **No serious medical condition that would interfere with participation in the study (e.g. that would prevent breastfeeding or adherence to the follow-up schedule), as judged by the on-site clinician.**

## 9. Maternal Screening Procedures

*Section 2.1, Maternal Screening, Enrollment and Follow-Up, 3<sup>rd</sup> paragraph:* Described below are the required clinical and laboratory procedures for mothers; see also Appendix I A for a schedule of maternal evaluations. HIV-infected 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 3 after birth. **At screening** ~~women screened prior to delivery will~~ **undergo** ~~have~~ medical history and physical exam, **as outlined in the Study Specific Procedures (SSP) Manual** ~~documented for study purposes~~ and will undergo one blood draw for CBC with differential, CD4+ cell count, stored plasma for later NVP resistance, HIV-1 RNA PCR testing. **Women that are screened prior to A+ labor and delivery will repeat the clinical and laboratory procedures at labor and delivery** (on or before day 3 post delivery). ~~blood will be drawn for CBC with differential, CD4+ cell count, and plasma (storage for NVP resistance and HIV-1 RNA PCR testing).~~ Post delivery.....

## 10. Ability to Breastfeed:

*Section 4.2, Infant Randomization Criteria:* Following “Infants must be randomized on or before day 3 post delivery. Infants must meet the following criteria for randomization:” a fourth bullet was added:

- **Able to breastfeed (i.e., mother and infant alive with no condition apparent that would preclude breastfeeding)**

Under “Infants who meet any of the following criteria will be excluded from randomization:” the first bullet was deleted:

- ~~Not able to breastfeed (e.g. mother died or otherwise unable or unwilling to breastfeed despite original intentions)~~

## 11. Descriptive Definition of Clinical Hepatitis:

*Section 4.2, Infant Randomization Criteria:* Under “Infants who meet any of the following criteria will be excluded from randomization:” the second bullet was modified as follows:

- Confirmed or suspected clinical hepatitis, defined as clinical signs and symptoms of clinical hepatic dysfunction including **but not necessarily limited to** enlarged liver (>4 cm below right costal margin), hepatic tenderness **and/or** ascites, ~~portal hypertension (e.g., varices, splenomegaly, caput medusae), or hepatic encephalopathy (e.g., asterixis, changes in level of consciousness)~~

The same wording change was made in the footnote to the Toxicity Management Table, Appendix IV.

**12. Multiple Births:**

*Section 4.2, Infant Randomization Criteria:* The following sentence has been added to the end of the section: In the case of a multiple birth, infants will be included in the study only if both/all are eligible and will be randomized to the same study arm. **If only one infant of a multiple birth is alive, the infant may be enrolled if he/she otherwise meets all of the criteria.**

**13. Maternal Testing Requirements:**

*Section 5.3, Maternal Evaluations in the Case of Early Withdrawal, bullet 3:* Plasma storage for ~~NVP concentration~~ **HIV-1 RNA PCR** and **NVP resistance**

**14. Concomitant Medications:**

*Section 5.8, Infant Concomitant Medications, sentence 1:* Infant systemic medications including only antibiotics, antiretrovirals, antifungals, and antimicrobicides used in infants will be recorded on applicable study case report forms through ~~8 weeks post dosing~~ **months of life.**

**15. Re-Dosing of Infants:**

*Section 6.2, Treatment Dose and Administration:* The following sentence has been added: **Any infant who vomits within 60 minutes of study drug dosing may re-dosed one time following the first dose.**

**16. Study Drug Dosing:**

- *Section 6.2.1, Conditions for Exclusion from Initial Study Drug Dosing:* The following note has been added at the end of this section:

**Note: Mothers will be instructed to begin administration of the study drug to the infant on Day 5 after birth ( $\pm 2$  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, the procedures below will be followed:**

- **If within four weeks ( $\leq 28$  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.**
- *Section 6.2.2, Conditions for Exclusion from Subsequent Doses of Study Drug:* The following note has been added after the existing list of bullets:

**Note: Infants with a gap in study drug dosing of more than four consecutive weeks ( $> 28$  days) must have a negative HIV DNA PCR result on a specimen obtained at the study visit when the gap was identified or within the prior two weeks or dosing cannot be resumed.**

Resumption of study drug dosing following a gap is to be at the level appropriate for the infant's age.

17. Title of Standard DAIDS Toxicity Table:

- *Section 6.2.1, Conditions for Exclusion from Initial Study Drug Dosing, sentence 1:* See Section 7.0 and the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004, (which can be found in the Study Specific Procedures (SSP) Manual and at the following website: <http://rcc.tech-res-intl.com>).
- *Section 7.1, Severity Grading, paragraph 1, sentence 1:* Severity of all AEs will be graded according to the standard DAIDS Toxicity Tables for infants <3 months and children >3 months of age, Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004, (which can be found in the SSP Manual and at the following website: <http://rcc.tech-res-intl.com>).

18. DNA PCR Result:

*Section 6.2.1, Conditions for Exclusion from Initial Study Drug Dosing: paragraph 3:* If any of the conditions bulleted below are known prior to dosing in an infant who has been randomized, the first dose of study drug should be withheld and the following procedures should be followed. **As specified in Section 4.2, results of the laboratory tests are not required prior to randomization or dispensing of study drug.** If the mother has left the clinic with the study drug, study staff will attempt to contact her, and she will be instructed to withhold dosing and to return to the clinic for a repeat blood test and/or further clinical assessments.

The following condition has been added to the existing bullets:

- **Initial HIV DNA PCR from birth specimen is positive**

19. Adverse Event Reporting:

*Section 7.0, Safety Monitoring and Adverse Event Reporting, paragraph 3:* The first and second sentences of paragraph 3 have been moved to the end of the paragraph for clarity; only changed text is noted below in bold or strike-through.

~~Throughout the entire 18-month follow-up period, SAEs that are judged by the on-site study clinician to be possibly, probably or definitely related to the study drug, or for which a relationship cannot be determined will also be reported on~~ **The expedited adverse event (EAE) reporting requirements and definitions for this study and the methods for expedited reporting of AEs to the DAIDS Regulatory Compliance Center (RCC) Safety office are defined in the “The Manual for Expedited Reporting of Adverse Events to DAIDS” (EAE Manual), dated 6 May 2004, . The DAIDS EAE Manual is available on the RCC website: <http://rcc.tech-res-intl.com>.**

**Adverse events that meet the criteria for expedited reporting as specified in the EAE Manual or this protocol will be reported on the standard DAIDS SAE Expedited Adverse Event Report Form (EAE Reporting Form) available on the RCC website: <http://rcc.tech-res-intl.com> and sent within three days of site awareness to the DAIDS Adverse Experience Reporting (AER) RCC Safety Office.**

Specifically, the ‘Standard Level’ of expedited AE reporting as defined in the DAIDS EAE Manual will be applied. In addition, as a protocol-specific requirement, all grade 3 and 4 rashes and grade 3 and 4 ALT levels, regardless of seriousness or relatedness, will be reported in an expedited manner to DAIDS.

**AEs that meet the criteria for expedited reporting must be reported to the DAIDS RCC Safety Office on an expedited basis, during the protocol defined EAE Reporting Period, which is the entire duration of each infant’s follow-up period (from randomization/study enrollment until study completion or discontinuation of the infant from study participation for any reason). After the end of the protocol-defined EAE reporting period stated above, sites must report to the DAIDS RCC Safety Office unexpected, serious adverse drug reactions if the study site staff become aware of the event on a passive basis, i.e., from publicly available information.**

Information on all non-serious and serious AEs in infants through 8 months of life (8 weeks after maximum study dosing duration) - regardless of relatedness - will be recorded in the participant source records and on standard DataFax AE case report forms (CRFs) for entry into the study database. After 8 months of life, information on all concurrent illnesses will be recorded in the participant source records, but only SAEs **and AEs that otherwise meet the criteria for expedited reporting to DAIDS (including grade 3 and 4 skin rash and grade 3 and 4 ALT)** will be reported on standard DataFax AE CRFs for entry into the study database. **These reporting requirements are summarized in Appendix V.**

The following typical childhood illnesses will be recorded in participant source records and captured in the study database as interim medical history or physical examination findings, but will not be reported separately as adverse experiences: diaper rash, otitis media, and afebrile upper and lower respiratory tract infections including bronchiolitis. However, if one of these conditions results in death, it will be reported as an SAE according to the procedures outlined above.

**The study drug that must be considered in determining relationships of AEs in HPTN 046 is the daily nevirapine ((NVP)Viramune) or nevirapine ((NVP)Viramune) placebo regimen begun in infants at 5 days after birth ( $\pm 2$ ) days. Conditions or illnesses in infants occurring before randomization will be reported as pre-existing conditions, including congenital anomalies.**

## **20. Confidentiality of Study Records:**

*Section 9.5, Confidentiality, paragraph 1:* All study-related information will be stored securely at the study site. All participant information will be stored securely in areas with access limited to study staff. To maintain participant confidentiality a coded number will identify all study specific laboratory specimens, reports, study data collection, process, and administrative forms. ~~All study records that contain names or other personal identifiers will be stored separately from other study records.~~ **Study-specific laboratory specimens, case report forms or documents that are transferred or transmitted off-site for processing will be identified by a coded number only, to maintain participant confidentiality.** All local databases will be secured with password-protected access systems. ~~Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate area with limited access.~~ **The use of participant identifiers on study records will comply with the DAIDS SOPs for Source Documentation and Essential Documents.**

## 21. Viral Load Assays:

*Section 10.1, Local Laboratory Specimens:* The following has been added after the list of assays to be performed locally: **Note: Site labs that meet the ongoing assay certification requirements overseen by the CL may also perform the plasma HIV-1 RNA assays locally.**

## 22. Location of Study Specific Procedures Manual

*Section 11.2, Study Coordination, paragraph 1:* This protocol will direct study implementation. In addition, a Study Specific Procedures (SSP) Manual, will outline procedures for conducting study visits; data and forms processing; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations. The SSP Manual will be submitted to the sponsor prior to implementation of the study, **will be posted on the following website: <http://www.HPTN.org>** and will be made available in hard copy to the IRBs/ECs, the US FDA and other regulatory authorities upon request.

## 23. Sample Study Enrollment Informed Consent Form:

- *Section 9.2, Informed Consent, sentence 2:* **If he is reasonably available at the study clinic, the study will also be thoroughly explained to the father and his written informed consent obtained; however, the father's written consent is not required for enrollment of the mother or infant, unless otherwise directed by the IRB/EC overseeing research at the site.**
- *Appendix IIA, Introduction, paragraph 2:* Before you decide whether or not to take part in this research study, you need to know the purpose, the possible risks and benefits to you and your baby and what will be expected of you and your baby. The study staff will discuss this with you. They will answer any questions that you have. After the study has been fully explained to you, you can decide whether or not you want to participate. Once you understand the study, and if you agree to take part, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy to keep. **You are encouraged to bring the baby's father to the study clinic so that we can also explain the study to him. If the father of your baby is available and comes to the study clinic to participate in the informed consent discussion, he will be asked to sign the consent form also.**

*Mother's Procedures, paragraph 2:* Screening Procedures: If you agree to take part in this study and sign the informed consent form, we will first need to determine if you and your baby are eligible. This will include asking you some questions about your health and doing a physical examination. Some people may not be eligible for 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 equal to about** one tablespoon) to check your health and to be stored for later HIV-related tests.

*Mother's Procedures, paragraph 3:* If you have not already delivered your baby, you will be instructed to come the clinic as soon as your labor contractions begin. You will come to this hospital or clinic to give birth to your baby. When you arrive, you will be asked questions about your health and be asked to give a blood sample (about 10 ml which is **less than equal to about** one tablespoon) to check your health and to be stored for later HIV-related tests. **You will have physical examination soon after delivery (within 3 days).** The study staff will inform you if you and your baby are eligible for the study.

*Mother's Procedures, paragraph 6:* At some of the study visits, you will give a blood sample (about 15 ml, which is equal to about 1 tablespoon) to check your health. **Some of the blood may be stored for later HIV-related study tests.** You will be asked to give a sample of breast milk (20 ml, which is less than 2 tablespoons), to be stored for later HIV-related study tests. At all of the visits, you will have a physical exam and will be asked about your health. You will be given the results of all tests done during the study related to your health **when the results are available - usually at the next study visit.**

*Baby's Procedures, paragraphs 1 and 2:* At birth, **your baby will have a physical examination.** Your baby's health and weight will be checked to be sure that he or she is eligible for the study and a small amount of blood will be drawn (about 5 ml or one teaspoon). If you and your baby are eligible for the study, you will be asked to give your baby the study syrup every day for the first 6 months of life or as long as you are breastfeeding. If you choose to completely stop breastfeeding your baby before 6 months, you will also stop giving your baby the study syrup.

**At each scheduled study visit, your baby will have a physical examination.** At some of the study visits your baby will have a small blood sample (about 5 ml, which equals one teaspoon) taken to check his or her health. You will be given the results of all tests performed during the study that are related to your baby's health **when the results are available - usually at the next study visit.** Some of the blood taken will be tested for HIV. Your baby will be tested for HIV about ~~8~~ 7 times over the 18-months of the study. **Some blood will be stored for later HIV-related study tests.** If one of the tests shows that your baby may be infected with HIV, a second test will be done to confirm this result. If your baby is found to be HIV infected, you will be informed as soon as possible. You will stop giving your baby the study syrup. However, you and your baby will remain in the study and be asked to return for all study visits as scheduled.

*Risks and/or Discomforts, paragraph 1:* A number of serious side effects have been associated with nevirapine used in adults and children for treatment of HIV. ~~However, these side effects have only been reported with use of much higher doses of nevirapine than will be used in this study.~~ These side effects include inflammation of the liver that in rare cases may lead to severe or life-threatening liver damage and death. An infant with liver disease may seem tired or sleepy, feed poorly, have pale stool, darkened urine, yellowing of the eyes or skin, tenderness of the liver, or abnormal tests of the liver. An infant with active hepatitis B or C infection or abnormal liver tests is at higher risk for worsening liver disease. **While these side effects have only been reported with use of much higher doses of nevirapine than will be used in this study, we do not know whether the dose of nevirapine used in this study could result in these conditions.**

*Risks and/or Discomforts, Paragraph 5, sentence 3:* At these doses, we do not expect babies to experience bad effects from this drug, **but we do not know this for sure.**

*Risks and/or Discomforts, Paragraph 6, sentence 3:* Redness, pain in the area or a bruise may form and swelling **or infection** may occur where the needle goes into your baby's skin.

*Costs to You, paragraph 2:* **Antiretroviral treatment for HIV will not be provided through this study. However, you and your baby, if he or she is found to be infected with HIV, will be referred to available care and treatment programs for which you might qualify.**

**24. Severity Grading for Malnutrition and Fever:**

*Appendix III* - Title and table were modified as shown below to include malnutrition and fever (The scale for cutaneous/skin rash/dermatitis included in the table remains unchanged.) Section 7.1, paragraph 2, was also modified to reflect this addition where the supplemental grading table is referenced.

**SUPPLEMENTAL TABLE FOR GRADING THE SEVERITY OF CUTANEOUS/SKIN RASH/DERMATITIS, MALNUTRITION AND FEVER**

GRADE 1	GRADE 2	GRADE 3	GRADE 4
<b>MALNUTRITION (FAILURE TO THRIVE)</b>			
<b>UNDERWEIGHT:</b> 60-80% of the 50th percentile expected weight for age AND Edema Absent	<b>MARASMUS:</b> <60% of 50th percentile expected weight for age AND Edema Absent	<b>KWASHIORKOR:</b> 60-80% of the 50th percentile expected weight for age AND Edema Present	<b>MARASMIC-KWASHIORKOR:</b> <60% of 50th percentile expected weight for age AND Edema Present
<b>FEVER (AXILLARY)</b>			
37.1 - 38.0°C	38.1 - 38.7°C	38.8 - 39.9°C	>39.9°C

**25. Toxicity Management:**

*Appendix IV, Table of Toxicity Management Procedures*, has been revised as follows:

CONDITION	SEVERITY <sup>1</sup>	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT <sup>2</sup>
<b>HEPATIC TOXICITY MANAGEMENT</b>			
Suspected clinical hepatitis <sup>33</sup>	Any Grade	Hold study drug (regardless of ALT grade)	Observe and evaluate.  If clinical hepatitis is confirmed, study drug should be permanently discontinued.  If clinical hepatitis is ruled out <b>and ALT is Grade 1 or lower, has returned to baseline</b> study drug can be <del>restarted</del> <b>reintroduced after consultation with and permission from the Protocol Safety Review Team.</b>
Asymptomatic ALT	Grade 2	May be continued or held pending repeat assessment based on the clinician's judgment.	Repeat laboratory assessment as soon as possible, ideally within 72 hours.  <b>If repeat assessment confirms Grade 2 toxicity AND no alternative explanations for the abnormality can be determined, hold study drug and reassess for up to 21 days. If Grade 2 toxicity persists at approximately 21 days, permanently discontinue study drug. If repeat assessment is Grade 1, study drug may be continued or reintroduced.</b>  If definitive alternative explanation for the abnormality has been determined, then study drug can be continued or reintroduced after ALT returns to Grade 1 or less after consultation with and permission from the Protocol Safety Review Team.  If Grade 2 or higher toxicity recurs in a participant whose ALT had resolved to Grade 1 or less, study drug should be permanently discontinued.

CONDITION	SEVERITY <sup>1</sup>	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT <sup>2</sup>
Asymptomatic ALT	Grade 3 or 4	Hold	<p>Repeat laboratory assessment as soon as possible, ideally within 72 hours.</p> <p><del>If repeat assessment is Grade 2 or less. Study drug may be restarted.</del></p> <p><del>If repeat assessment confirms Grade 3 or higher toxicity. Continue to hold study drug and re-evaluate.</del></p> <p><del>If Grade 3 or higher toxicity recurs in a participant who returned to Grade 2 or less, study drug should be permanently discontinued.</del></p> <p><b>If repeat assessment confirms Grade 3 or higher toxicity AND no alternative explanation for the abnormality can be determined, then study drug should be permanently discontinued.</b></p> <p><b>If repeat assessment confirms Grade 2 toxicity AND no alternative explanations for the abnormality can be determined, hold study drug and reassess for up to 21 days. If Grade 2 toxicity persists at approximately 21 days, permanently discontinue study drug. If repeat assessment is Grade 1, study drug may be reintroduced.</b></p> <p><b>If repeat assessment is Grade 2 or above AND a definitive alternative explanation for the abnormality has been determined, then study drug can be reintroduced after ALT resolves to Grade 1 or less after consultation with and permission from the Protocol Safety Review Team.</b></p> <p><b>If Grade 2 or higher toxicity recurs in a participant whose ALT had resolved to Grade 1 or less, study drug should be permanently discontinued.</b></p>
<b>SKIN RASH MANAGEMENT</b>			
Erythema with or without pruritus <del>during first 2 weeks of study treatment</del>	Grade 1	May be continued <b>or held pending repeat assessment based on the clinician's judgment.</b>	<p>Pruritis and minor accompanying symptoms may be managed with antihistamines, antipyretics and/or non-steroidal anti-inflammatory medications. If rash does not resolve within 14 days of onset, contact Protocol Safety Review Team.</p> <p><b>If there is no definitive explanation for the rash/skin reaction (e.g., infant acne, diaper rash, varicella), the infant must have ALT drawn, assayed, and value reviewed (management for ALT as per hepatic toxicity management). If there is a definitive alternative diagnosis for the rash, then ALT does not need to be measured.</b></p>
Diffuse erythematous macular or maculopapular rash or dry desquamation with or without pruritus but without constitutional findings or target lesions without blister/vesicle or ulceration in lesion	Grade 2A	May be continued <b>or held pending repeat assessment based on the clinician's judgment.</b>	<p><del>As above; however if rash occurs within the first two weeks of life, the dose should remain at 0.6ml per day and not be escalated until the rash resolves.</del></p> <p><b>Same management as per Grade 1</b></p>
Urticaria	Grade 2B	<del>May be continued</del> <b>Hold</b>	<p><del>As above; however, if study drug is interrupted DO NOT reintroduce</del></p> <p><b>If there is no definitive explanation for the rash/skin reaction (e.g., infant acne, diaper rash, varicella), the infant must have ALT drawn, assayed, and value reviewed (management for ALT as per hepatic toxicity management). If there is a definitive alternative diagnosis for the rash, then ALT does not need to be measured.</b></p> <p><b>If a definitive alternative explanation for the rash/skin reaction <u>cannot</u> be determined, study drug should be permanently discontinued.</b></p> <p><b>If rash/skin reaction is definitely due to a definitive alternative diagnosis, study drug may be reintroduced after consultation with and permission from the Protocol Safety Review Team AND the rash has resolved.</b></p>
Grade 3 (A through E) <del>or</del> 4-Skin rashes		<del>Immediate and permanent discontinuation</del> <b>Hold</b>	<b>Same management as for Grade 2B above.</b>
<del>Grade 3 or</del> Grade 4 Skin rashes		Immediate and permanent discontinuation	

CONDITION	SEVERITY <sup>1</sup>	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT <sup>2</sup>
<b>EVENTS OTHER THAN HEPATIC TOXICITY OR RASH MANAGEMENT</b>			
Any Grade 1 or 2 event other than hepatic or rash		Continue study drug.	
Any Grade 3 event other than hepatic toxicity or rash		May be continued or held pending repeat assessment based on the clinician's judgment	<p>Repeat assessment as soon as possible, ideally within 72 hours.</p> <p>If repeat assessment is Grade 2 or less, study drug may be <b>continued or restarted</b>.</p> <p>If repeat assessment confirms Grade 3 toxicity AND <b>no</b> alternative explanations for the abnormality <del>can be have not been</del> determined, hold study drug, <b>obtain ALT measurement and reassess</b> for up to 7 21 days <del>and reassess</del>: <b>(manage ALT levels as per hepatic toxicity management)</b>. If Grade 3 or higher toxicity persists <b>at approximately 21 days, or recurs and alternative explanations for the abnormality have not been determined</b>: study drug should be permanently discontinued. <b>If Grade 3 abnormality resolves to Grade 2 or lower within 21 days, study drug may be reintroduced. If Grade 3 toxicity recurs, study drug should be permanently discontinued.</b></p> <p><b>If repeat assessment confirms Grade 3 AND a definitive alternative explanation for the abnormality has been determined, study drug can be continued or reintroduced after consultation with and permission from the Protocol Safety Review Team.</b></p> <p><del>Note: If alternative explanations for the abnormality have been determined then study drug may be continued.</del></p>
Any Grade 4 event <b>that is not immediately life threatening</b> other than hepatic toxicity or rash		Hold	<p>Repeat assessment as soon as possible, ideally within 72 hours.</p> <p><b>If repeat assessment is Grade 2 or less, study drug can be reintroduced.</b></p> <p><b>If repeat assessment shows Grade 3 or higher toxicity, manage as per Grade 3 toxicity management.</b></p> <p>If repeat assessment confirms Grade 4 toxicity AND <b>no alternative explanation for the abnormality can be determined</b>, study drug should be permanently discontinued.</p> <p><b>If repeat assessment is Grade 4 AND a definitive alternative explanation for the abnormality has been determined, study drug can be reintroduced after consultation with and permission from the Protocol Safety Review Team.</b></p>
Any Grade 4 event that is immediately life threatening		<b>Immediate and permanent discontinuation</b>	

<sup>1</sup>See Section 7.0 the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events and Appendix III for grading criteria.

<sup>2</sup>If study drug is stopped due to toxicity, participant should have repeat clinical or laboratory evaluations every 10-14 days, if possible, until toxicity resolves.

<sup>3</sup>Clinical Hepatitis is defined as clinical signs and symptoms of clinical hepatic dysfunction regardless of ALT values, including **but not necessarily limited to** enlarged liver (> 4cm below right costal margin), hepatic tenderness, **and/or** ascites, ~~portal hypertension (e.g., varices, splenomegaly, caput medusae), or hepatic encephalopathy (e.g., asterixis, changes in level of consciousness).~~

26. Addition of AE Reporting Table:

APPENDIX V: HPTN 046 Adverse Event Reporting and Documentation Requirements\*

	ADVERSE EVENT	RELATIONSHIP TO STUDY PRODUCT	REQUIRED REPORTING DURATION	AE LOG CRF (DataFax to SDMC)	EAE FORM (to DAIDS RCC within 3 business days of site awareness)
SERIOUS ADVERSE EVENTS	Results in Death	Regardless of relationship	Duration of study	YES	YES
	Results in persistent or significant disability or incapacity	Regardless of relationship	Duration of study	YES	YES
	Requires or prolongs hospitalization	Probably not related Possibly related Probably related Definitely related	Duration of study	YES	YES
	Requires intervention to prevent significant incapacity/permanent disability or death	Probably not related Possibly related Probably related Definitely related	Duration of study	YES	YES
	Is immediately life-threatening	Probably not related Possibly related Probably related Definitely related	Duration of study	YES	YES
	All other SAEs	Not related to study product	Duration of study	YES	NO (unless directly related to study participation)
NON-SERIOUS ADVERSE EVENTS	Grade 3 or 4 skin rash**	Regardless of relationship	Duration of study	YES	YES
	Grade 3 or 4 ALT**	Regardless of relationship	Duration of study	YES	YES
	All other non-serious AEs	Regardless of relationship	Through 8 months of life	YES	NO

\* All AEs must be documented in the participant's source record for the duration of the study, regardless of seriousness, severity or relatedness.

\*\*These events could be serious; refer to definition of SAE. Regardless, they are considered EAEs in HPTN 046.

## APPENDIX A – Summary of Changes to Background Text

### Revised HPTN 046 Background Sections

Added text appears in bold, and deleted text is indicated by strike-through.

*Section 1.1.3, Preliminary SIMBA and Mashi Study Results:* The following text was added as paragraphs 4, 5 and 6 of this section:

**More recently, data have been presented from the Mashi Study, conducted in Botswana (32). This study was a factorial design in which mother-infant pairs were randomized by feeding strategy and then randomized again by whether they receive single-dose mother/infant NVP or placebo. In this study, all HIV-infected women received ZDV starting at 34 weeks gestation and orally intrapartum, and all infants received one month of ZDV; infants were randomized to formula feed (with one month of ZDV) or to breastfeed with six months of infant ZDV prophylaxis. The median duration of breastfeeding was 5.8 months, almost three months longer than in the SIMBA study.**

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

**The overall transmission rates were similar in the SIMBA (8%) and Mashi (9%) studies. Like SIMBA, the lack of a control group in the Mashi study makes the data inadequate to accurately assess the potential efficacy of infant prophylaxis. However, in the Mashi study, the fact that the infection rate at age seven months in the breastfeeding group, in which six months of infant ZDV prophylaxis was given, was significantly higher than in the formula feeding arm is of concern. Additionally, the Mashi 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. 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 Nevirapine. 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 Mashi studies, any design other than the most rigorous and appropriate (randomized, placebo-controlled), will not yield conclusive results with practical implications that are informative to policy makers, health care organizations/providers and donors.**

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### *Section 1.4.3, Safety of NVP Used for Treatment of HIV Infection, beginning at paragraph 1:*

The most frequently reported adverse experiences related to NVP are rash, fever, nausea, headache and abnormal liver function tests (35,36). **The toxicities of greatest concern with chronic NVP therapy are hepatic toxicity, severe skin reactions, and hypersensitivity.**

Severe, life threatening, and, in some cases, fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, have been reported in patients treated with NVP. **Grade 3 or 4 ALT elevations have been reported in approximately 6-17% of HIV-infected adults receiving NVP-based therapy (66-69); acute symptomatic hepatitis occurs less frequently, in approximately 1-3% of patients (67, 68, 70). In clinical trials, the risk of hepatic events regardless of severity in patients receiving NVP was greatest in the first six weeks of therapy. However, the risk of any hepatic event, with or without rash, continues past this period and may occur at any time during treatment. In some cases, patients presented with non-specific, prodromal signs or symptoms of hepatitis, including fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum ALT levels. Some of these events have progressed to hepatic failure with ALT elevation, with or without hyperbilirubinemia, prolonged partial thromboplastin time, or eosinophilia. In some cases, hepatic injury has progressed despite discontinuation of treatment; this is likely due to the very long half-life of NVP, with drug levels that can persist as long as two weeks following discontinuation.**

**Symptomatic hepatic events are often associated with rash or other signs of hypersensitivity reaction, including fever. Adult women and patients with higher CD4+ counts are at increased risk of these hepatic events. Women with CD4+ counts >250 cells/mm<sup>3</sup> are at considerably higher risk of these events. In clinical trials the overall NVP-attributable risk of hepatitis is approximately 1%.** Increased transaminase (ALT) values before starting therapy or history of hepatitis B or C infections have been associated with a greater risk of hepatic adverse experiences in patients on chronic NVP therapy (66). ~~Acute hepatotoxicity has progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, prolonged prothrombin time or eosinophilia. Hepatic dysfunction can be isolated or associated with signs of hepatotoxicity. Serious hepatic events occur most frequently during the first 12-16 weeks of NVP therapy, and have been reported to occur as early as within the first few weeks of therapy. Approximately one-third of cases have occurred after the critical 12-week period. NVP should be discontinued and not be restarted following severe hepatic, skin or hypersensitivity reactions.~~

Severe, life-threatening skin reactions, including fatal cases, have been reported with NVP therapy, occurring most frequently during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Rashes are usually mild to moderate maculopapular erythematous cutaneous eruptions with or without pruritus and located on the trunk, face and extremities. Stevens-Johnson syndrome has occurred in 0.3% of 2861 **HIV-infected** adult patients exposed to NVP (71). Dose escalation, using a lower “lead-in” dose of NVP for the first two weeks of therapy, has been shown to reduce the frequency of NVP-associated rash.

NVP has occasionally been given to HIV-uninfected individuals, **the vast majority adults**, as post-exposure prophylaxis (PEP) for occupational and non-occupational exposures to HIV. When given as PEP, NVP is administered for four weeks in standard doses used for treatment of HIV-infected individuals, ~~and often given without the 2-week induction period recommended for treatment. There have been twelve cases of reported hepatotoxic reactions among these individuals; one developed liver failure (requiring liver transplantation), seven had clinical hepatitis and four had elevations in serum liver~~

## APPENDIX A – Summary of Changes to Background Text

enzymes without reports of clinical hepatitis. Data on the number of persons taking NVP for PEP is insufficient to calculate accurate rates of adverse event (65). **In a review of the FDA voluntary adverse event reporting system, there have been 12 cases (11 in adults, 1 in a child) of severe cutaneous toxicity in non-HIV-infected persons receiving PEP, including three with Stevens-Johnson syndrome; these reactions occurred after 7 to 12 days of NVP-containing PEP regimens (72). After discontinuation of NVP, all affected individuals rapidly improved. Additionally, 30 non-HIV-infected individuals (all adults) developed hepatotoxicity after 8 to 35 days of a NVP-containing PEP regimen. Findings included grade 3 or 4 hepatotoxicity (n=14), fever (n=11), skin rash (n=8), eosinophilia (n=6), and fulminant hepatic necrosis requiring a liver transplant (n=1) (72). After discontinuation of NVP, all but two of these individuals improved in a median of 22 days; in one individual, hepatic toxicity resolved in three months, while in the other, liver transplant was required. In a study of 41 non-HIV-infected adult volunteers in a phase I study of NVP, four (10%) developed grade 1 or 2 hepatic toxicity and another four (10%) developed grade 3 or 4 hepatic toxicity; all cases reversed with discontinuation of drug (72). In a study in London of uninfected individuals receiving NVP PEP, a 20% rate of grade 3 or 4 hepatic toxicity was reported (73). It should be noted that all reported cases of severe hepatic toxicity occurred in uninfected adults; however, the number of uninfected children receiving PEP would be expected to be small. Although precise estimates of the risk for severe hepatic toxicity are not available, the risk appears to be higher in adults who do not have HIV infection and may be an immunologic-based phenomenon, as it is associated with higher CD4 counts among HIV-infected adults.**

**In children, the most common reported adverse effects with chronic NVP therapy has been rash and granulocytopenia.** In initial clinical trials of NVP treatment in HIV-infected children, rash was observed in 24% (36). When a two-week lower dose "lead in" period was used, the incidence of rash was decreased (58). While grade 2 or higher skin rash has been reported in up to 33% of children receiving NVP (71), serious rash is less common. In a study of 4-drug therapy including NVP (given with two-week lead in), serious rash was observed in 6% of children (75). In another study of NVP-based therapy in 74 HIV-infected children **in the United Kingdom**, rash occurred in 20% of patients but serious grade 3 or 4 rash occurred in only 5% (76). Granulocytopenia has also been reported in children receiving NVP (77); in the above study in 74 children, 7% of children had grade 3 or 4 neutropenia, and in other studies neutropenia has been reported in 9% to 38% of children receiving NVP (74, 77). However, it should be noted the children in these studies were also receiving nucleoside analogue reverse transcriptase, such as ZDV, a known cause of granulocytopenia.

**In the published literature, hepatic toxicity appears to be much less frequent in HIV-infected children receiving chronic NVP therapy than the 6-17% rate of grade 3 or 4 ALT elevations reported in HIV-infected adults. In the study of 74 HIV-infected children receiving chronic NVP therapy, only one child (1%) developed grade 3 or 4 elevated ALT levels; this child had concomitant hepatitis C infection (76). In PACTG 356, 52 HIV-infected infants received 3- and 4-drug NVP-based therapy initiated between two weeks and two years of age and were followed for 200 weeks; liver function tests were performed at baseline and every four weeks through week 24, every eight weeks through week 56, then every 12 weeks (78). There were 26 grade 3 or 4 adverse events possibly related to the study regimens in 8 children (15%). These events were rash (four events in three children), neutropenia (17 events in four children), or anemia (two events in one child). No grade 3 or 4 elevations in ALT levels or symptomatic hepatitis were observed.**

**Administration of NVP to children without HIV infection is unusual. As discussed above, among uninfected individuals receiving PEP who had adverse events, only one case (rash) was reported in a child, and all the hepatic adverse events were in adults. NVP has been administered to uninfected**

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infants in HIVNET 023 and SIMBA. HIVNET 023 (discussed in more detail in Section 1.5) enrolled 75 infants born to HIV-infected women and evaluated the pharmacokinetics and safety of daily, twice weekly, and once weekly NVP administration for the first 6 months of life (79). Serum ALTs were monitored at birth and ages 2, 4, 8, 12, 20, 24 and 32 weeks. No grade 3 or 4 laboratory hepatic toxicity was observed in 36 infants (12 in each dosing group) at the Zimbabwe site; there were no clinical hepatic toxicities other than two HIV-infected infants who had hepatomegaly. There were three deaths (4% of 75 patients, one in each dosing group), none drug-related (one infant with early onset sepsis and two with pneumonia). In the SIMBA study, discussed in Section 1.1.3, 198 HIV-exposed infants received 6 months of once daily NVP and 199 received daily 3TC for prophylaxis of breast milk transmission. Grade 3 or 4 elevations in hepatic ALTs were observed in 3 infants receiving NVP (1.5%) and 2 infants receiving 3TC (1.0%) (personal communication to Dr. Katzenstein from Drs. Hassink and Luchters on behalf of SIMBA team, 12/09/03; frequency of monitoring not provided). There were eight infant deaths in the NVP group (five in the 3TC group); two of these deaths were in infants with documented HIV infection. None of the deaths were felt by the investigators to be related to study drug (however, etiologies were not provided).

New references added to Section 12:

31. Vyankandondera J, Luchters S, Hassink E, et al. Reducing risk of HIV-1 transmission from mother to infant through breastfeeding using antiretroviral prophylaxis in infants (SIMBA study), 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, France, July 13-16, 2003, Abstract LB7.
32. Shapiro, R, Thior I, Gilbert P, et al., Maternal Single-dose Nevirapine May Not Be Needed to Reduce Mother-to-Child HIV Transmission in the Setting of Maternal and Infant Zidovudine and Infant Single-dose Nevirapine: Results of a Randomized Clinical Trial in Botswana, 12th Conference on Retroviruses and Opportunistic Infections, Boston, MA, February 22-25, 2005, Abstract 74LB.
67. Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirine-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology* 2002;35:182-9.
68. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *JAIDS* 2004;35:538-9.
69. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis* 2005 (in press).
70. De Maat MMR, ter Heine R, van Gorp ECM, et al. Case series of acute hepatitis in a non-selected group of HIV-infected patients on nevirapine-containing antiretroviral treatment. *AIDS* 2003;17:2209-14.
71. Boehringer Ingelheim GmbH, Investigator's Brochure Nevirapine (BI-RG-587) Viramune, Version 6, March 2000.
72. Patel SM, Johnson S, Belknap SM, et al. Severe adverse cutaneous and hepatic toxicities associated with nevirapine use by non-HIV-infected individuals. *JAIDS* 2004;35:120-5.

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73. Benn PD, Mercey DE, Brink N, et al. Prophylaxis with a nevirapine containing triple regimen after exposure to HIV-1. *Lancet* 20001;357:687-8.
78. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med* 2004;350:2471-80.
79. Shetty AK, Coovadia HM, Mirochnick MM, et al. Safety and trough concentrations of nevirapine prophylaxis given daily, twice weekly, or weekly in breastfeeding infants from birth to 6 months. *JAIDS* 2003;34:482-90.

*Section 1.6 - Rationale for Infant Daily Dosing Regimen, Paragraph 3, next to last sentence:*

The mg/kg NVP dose approved for treatment of ~~HIV-infected infants~~ **pediatric patients 2 months up to 8 years** of age is 4 mg/kg once a day for the first 2 weeks of treatment followed by 7 mg/kg twice a day **thereafter**. The NVP doses in the above schedule will be administered once per day in ~~HIVNET-HPTN 046~~. ~~An infant weighing the same amount as the smallest HIVNET 012/023 infant would receive the largest mg/kg doses using the HIVNET 046 schedule. The total daily dose administered to these infants would be considerably less than the total daily dose approved for use in infected infants. An infant weighing as much as the heaviest HIVNET 012/023 infant would receive the smallest mg/kg NVP dose using the HIVNET 046 schedule. The daily dose arm of HIVNET 023 used mg/kg doses of 2 mg/kg for the first 2 weeks of life followed by 4 mg/kg from 2 weeks through 6 months. These doses produced NVP plasma concentrations well in excess of the therapeutic target of 100 ng/ml, so that the plasma concentrations achieved with the age-adjusted dosing schedule should well exceed the therapeutic target in the heaviest infants in HIVNET 046.~~

**Use of the chronologic dosing schedule based on age will result in a deviation in total daily dose from a weight-based dosing schedule. This deviation should not result in decreased efficacy or increased toxicity. The largest infants will receive the smallest per kg doses. Using the weight distribution of the HIVNET 012/023 infants, the smallest per kg daily doses with the chronologic schedule will be 56% of the HIVNET 023 weight-based doses (2.27 mg/kg vs 4.0 mg/kg at 6 weeks of age). There are no data describing the minimal effective concentration of NVP for prevention of HIV infection. In the absence of these data, 100 ng/ml (10 times the in vitro IC50 of wild type HIV) has been used as a minimum concentration target in developing NVP prophylactic regimens (PACTG 250, HIVNET 006 and 012). The median trough concentration achieved in HIVNET 023 with weight based dosing was 1348 ng/ml, so that adequate concentrations should be achieved with even the smallest per kg doses resulting from use of the chronologic dosing schedule.**

**The HPTN 046 dosing schedule should not result in excessive toxicity. The weight-based single daily dose regimen used in HIVNET 023 was well tolerated by study infants. Using the chronologic dosing schedule proposed for HPTN 046, the smallest infants will receive the largest per kg doses. Using the weight distribution of the HIVNET 012/023 infants, the maximum dose will be 7.5 mg/kg at age 14 weeks. This dose will be administered once a day in HPTN 046. The standard weight-based treatment dose for HIV infected children at this age is 7 mg/kg bid, which results in a total daily dose of 14 mg/kg - nearly twice as high as the maximum dose in HPTN 046.**