

## Protocol Clarification Memorandum #3 for:

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

DAIDS Document ID 10142

Clarification Memo Date: 23 November 2009

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#### *Summary of Revisions and Rationale*

In addition to the typical childhood illnesses specified in Section 7.0, the following childhood illnesses will not be reported as adverse events: infantile colic pain, oral thrush, gastrointestinal reflux and constipation. The exceptions are if these illnesses result in hospitalization or death. These illnesses will be recorded in participant source records and captured in the interim medical history and physical examination findings.

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#### *Implementation*

The procedures clarified in this memorandum have been approved by the NIAID Medical Officer. IRB approval of this Clarification Memorandum is not required by the sponsor prior to implementation; however sites may submit it to the responsible IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

The modification included in this Clarification Memorandum will be incorporated into the next full protocol amendment.

Text appearing below in bold will be added to the protocol.

*Section 7.0 Safety Monitoring and Adverse Event Reporting, paragraph nine.*

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, **infantile colic pain, oral thrush, gastrointestinal reflux, constipation** 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.

## **Letter of Amendment #2 for:**

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

**IND 72,592**

**DAIDS Document ID 10142**

**Letter of Amendment Date: 4 March 2009**

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

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

This Letter of Amendment (LoA) includes changes to the informed consent form for participants enrolled under Version 3.0 of the protocol. Participants enrolled prior to IRB/EC approval of this LoA need not be re-consented with the modified consent form, unless you are otherwise instructed by your IRBs/ECs; however, the new information contained therein must be provided to these participants as they return for follow-up, and this process must be documented. Your IRBs/ECs are responsible for determining how study participants are to be informed of the contents of this Letter of Amendment.

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

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

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#### ***Summary of Revisions and Rationale***

This Letter of Amendment includes no changes in participation requirements (e.g., volume or number of blood draws) or study procedures. The change included in Clarification Memorandum # 2, dated 20 February 2009, to Protocol HPTN 046 Version 3.0, dated 26 September 2007, has been included in this LoA.

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

1. As recommended by the NIAID Vaccine and Prevention Data and Safety Monitoring Board (DSMB), the informed consent form for participants enrolled under Version 3.0 of the protocol has been modified to include new information from other studies regarding the use of nevirapine for prevention of HIV transmission through breastfeeding.
2. It is clarified that the laboratory parameters on which infant enrollment criteria are based (ALT, hemoglobin, absolute neutrophil count and platelet count) can be re-assessed prior to final eligibility determination/enrollment if initial testing reveals exclusionary abnormalities in an infant otherwise likely to be eligible for study participation. The “birth specimen” is considered the final blood sample obtained on or before Day 7 of life that is used to confirm eligibility for enrollment. While this was the original intent and represents no change in study procedures, it was not explicitly stated in the current version of the protocol.

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### **Implementation**

The modifications detailed below will be formally incorporated into the body of the protocol with the next full amendment. *Deletions to the protocol text are indicated by strikethrough; additions are indicated in bold.*

- 1) Modifications to Informed Consent Form: Appendix II A, Sample Study Consent Form for Initial Enrollment Under Protocol Version 3.0 – *The affected sections are specified below.*

#### Purpose of the Study, paragraphs 4 and 5

A ~~recent~~ study conducted in Ethiopia, India and Uganda found that giving 6 weeks of the drug nevirapine once a day until the baby was 6 weeks old lowered the chance of passing HIV to the baby through breastfeeding. Because of these results, all babies who join this study will receive nevirapine once a day until the baby is 6 weeks old, even if this is not standard practice yet in this country. The study showed that using nevirapine until age 6 weeks reduces but does not completely prevent the chance of a mother passing the HIV virus to her baby. ~~It is not known if giving nevirapine to babies for a longer time would be even better in cutting the chance of passing HIV to the baby while breastfeeding.~~

We do not know **for certain** if nevirapine or any other drug given to the baby every day for more than six weeks is safe or if it will prevent a baby from getting infected with HIV while breastfeeding. **Other studies suggest that breastfeeding babies have some protection from HIV infection from breastfeeding while they are taking nevirapine. Thus, there is some suggestion that breastfeeding babies who take nevirapine for 6 months might be at lower risk of getting HIV from breastfeeding than they would be if they stopped taking nevirapine at 6 weeks of age. However, no one yet knows how long is best for breastfeeding babies to take nevirapine or any other drug to prevent transmission of HIV through breastfeeding.** This study will help find that out. Currently, the only certain way to prevent passing HIV through breastfeeding is not to breastfeed. As the counselors have discussed with you, there are health risks and benefits to both breastfeeding and not breastfeeding.

Risks and/or Discomforts, paragraph 1

**One half of the babies in this study will stop taking nevirapine after 6 weeks, while the other half will continue nevirapine until they are 6 months old. Other studies suggest that breastfeeding babies have some protection against HIV infection from breast milk while they are taking nevirapine. Thus, there is some suggestion that breastfeeding babies who take nevirapine for 6 months might be at lower risk of getting HIV from breast milk than if they stopped taking nevirapine at 6 weeks of age. However, no one yet knows how long is best for breastfeeding babies to take nevirapine, including how easy it will be to make sure that all babies in this country and other countries can get the right amount of nevirapine while they are breastfeeding. This study and others are trying to get enough information to help decide what is best for all babies in all countries.**

Alternatives to Participation, paragraph 1

You do not have to be in this study if you do not want to. The only known way to completely prevent passing HIV from a mother to her baby during breastfeeding is not to breastfeed. The clinic and study staff will explain the risks and benefits of breastfeeding to you and about safe alternatives. You will be provided information about where formula may be obtained. **If programs providing nevirapine or other drugs for prevention of HIV through breastfeeding become available in this area, the study staff will inform you.** The study staff will also refer you to HIV treatment programs that are available in your area. If you decide not to participate in the study, you will not lose the benefits of your standard medical care. You have a right to consider all options available to you and your baby.

- 2) Clarification Regarding Assessment of Infant Eligibility: *The following text (in bold) will be added after the last bullet:*

Section 4.2 Infant Enrollment Criteria

Infants who meet any of the following criteria will be excluded from enrollment into the study:

- ALT from birth specimen is Grade 2 or higher.
- Hemoglobin, absolute neutrophil count or platelet count from birth specimen is Grade 3 or higher
- Skin rash grade 2B (urticaria) or skin rash grade 3 or above
- 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.
- Serious illness or condition that would prohibit compliance with study procedures as judged by site clinician

**Note: Abnormal laboratory results as specified above (ALT, hemoglobin, absolute neutrophil count and platelet count) may be re-assessed as necessary on or before Day 7, and if the infant meets all the eligibility criteria, s/he can be enrolled. The “birth specimen” is considered the final specimen obtained on or before Day 7 of life that is used to confirm eligibility for enrollment.**

## **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**

**DAIDS DOCUMENT ID # 10142**

**A Study of the HIV Prevention Trials Network and the International Maternal, Pediatric and Adolescent AIDS Clinical Trials Network**

**Sponsored by:**

Division of AIDS, US National Institute of Allergy and Infectious Diseases  
U.S. National Institute of Child Health and Human Development  
U.S. National Institute on Drug Abuse  
U.S. National Institute of Mental Health  
U.S. National Institutes of Health

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Boehringer Ingelheim

**IND # 72,592**

**Protocol Chair:**

Hoosen M. Coovadia, MD, MBBS  
University of Natal  
Durban, South Africa

**Protocol Co-Chairs:**

Laura Guay, MD  
Johns Hopkins University  
Baltimore, MD

Wafaie Fawzie, MD, DrPH  
Harvard School of Public Health  
Boston, MA

Yvonne Maldonado, MD  
Stanford University School of Medicine  
Stanford, California

Daya Moodley, MSc, PhD  
University of Natal  
Durban, South Africa

**Clinical Sites:**

Prince Mshiyeni Hospital; Durban, South Africa

Muhimbili Hospital; Dar es Salaam, Tanzania

Mulago Hospital; Kampala, Uganda

Chitungwiza Clinics; Chitungwiza, Zimbabwe

and/or other DAIDS Clinical Trials Sites

**FINAL VERSION 3.0**  
**26 September 2007**

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**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**

**LIST OF ABBREVIATIONS AND ACRONYMS**

3TC	lamivudine
AE	adverse event
AFASS	acceptable, feasible, affordable, sustainable and safe
AIDS/HIV	Acquired Immunodeficiency Syndrome/ Human Immunodeficiency Virus
ALT	alanine aminotransferase
ART	antiretroviral therapy
AZT	azidothymidine
CBC	complete blood count
CI	confidence interval
CORE	(HPTN) Coordinating and Operations Center
CRF	case report form
CRPMC	Clinical Research Products Management Center
DAIDS	Division of AIDS
DSMB	Data Safety and Monitoring Board
ddI	didanosine
EC	ethics committee
EIA	enzyme immunoassay
FDA	(United States) Food and Drug Administration
HPTN	HIV Prevention Trials Network
IATA	International Air Transport Association
IFA	immunofluorescence assay
IRB	institutional review board
LDMS	Laboratory Data Management System
LL	local laboratory
mg	milligram
ml	milliliter
MTCT	mother-to-child HIV transmission
ng	nanogram
NL	(HPTN) Network Laboratory
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NICHHD	(United States) National Institute of Child Health and Human Development
NIH	(United States) National Institutes of Health
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NVP	nevirapine
NVPR	nevirapine resistance
PACTG	Pediatric AIDS Clinical Trials Group
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PSRT	Protocol Safety Review Team
SAE	serious adverse event
SDMC	(HPTN) Statistical and Data Management Center
SJS	Stevens-Johnson Syndrome
SSP	Study Specific Procedures Manual
UNAIDS	The Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
WB	Western blot
WHO	World Health Organization

## 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

#### PROTOCOL TEAM ROSTER

##### Protocol Chair

Hoosen Coovadia, MD, MBBS  
Victor Daitz Professor of HIV/AIDS Research  
Centre for HIV Networking (HIVAN)  
Nelson Mandela School of Medicine  
University of Natal  
719 Umbilo Road, Congella 4013  
Durban, South Africa  
Phone: 27-31-2604616  
Fax: 27-31-2604241  
E-mail: [coovadiah@nu.ac.za](mailto:coovadiah@nu.ac.za)

##### Protocol Co-Chairs

Laura Guay, MD  
Johns Hopkins University  
Carnegie 443  
600 North Wolfe Street  
Baltimore, MD 21287  
Phone: 410-502-3011  
Fax: 410-502-0688  
e-mail: [lguay@jhmi.edu](mailto:lguay@jhmi.edu)

Wafaie Fawzi, MD, DrPH  
Harvard School of Public Health  
Department of Nutrition  
6765 Huntington Ave SPH2-329A  
Boston, MA 02115  
Phone: 617-432-2086  
E-mail: [mina@hsph.harvard.edu](mailto:mina@hsph.harvard.edu)

Yvonne Maldonado, MD  
Stanford University School of Medicine  
300 Pasteur Dr. G-312b  
Stanford, CA 94305-5119  
Phone: 650-725-6565  
Fax: 650-725-8040  
E-mail: [bonniem@leland.stanford.edu](mailto:bonniem@leland.stanford.edu)

Daya Moodley, MSc, PhD  
Dept Obstetrics and Gynaecology  
Nelson R Mandela School of Medicine  
University of Natal  
Durban, 4051 South Africa  
Phone: 0927-31-2604432 or 0825507693  
Fax: 0927-31-2604241  
E-mail: [moodleyj@med.und.ac.za](mailto:moodleyj@med.und.ac.za)

##### Tanzania Investigator

Karim Manji, MBBS, Mmed  
Department of Pediatrics and Child Health  
Muhimbili University  
College of Health Sciences  
Dar es Salaam, Tanzania  
Phone: 255-22-2150503  
Fax: 255-22-2151394  
E-mail: [kmanji@muchs-harvard.org](mailto:kmanji@muchs-harvard.org)

##### Zimbabwe Investigators

Tsungai Chipato, MD  
UZ-UCSF Collaborative Research Programme  
15 Phillips Avenue Belgravia  
Harare Zimbabwe  
Phone: 263-4-704890 or -704920 or -722620  
Fax: 263-4-704897  
E-mail: [chipato@uz-ucsf.co.zw](mailto:chipato@uz-ucsf.co.zw)

Rose Kambarami, MBChB, DCH, FRCP, Mmed SC  
Department of Paediatrics and Child Health  
Medical School  
Box A 178 Avondale  
Harare Zimbabwe  
Phone: 263-4-791631  
Fax: 263-4-791995  
E-mail: [rosekamb@mweb.co.zw](mailto:rosekamb@mweb.co.zw)

Avinash K. Shetty, MBBS, DCH, MD, FAAP  
Associate Professor of Pediatrics  
Wake Forest University Health Sciences  
Medical Center Boulevard  
Winston-Salem, NC 27157  
Phone: 336-716-2740  
Fax: 336-716-7100  
Email: [ashetty@wfubmc.edu](mailto:ashetty@wfubmc.edu)

##### Uganda Investigator

Francis Mmiro, MBBS, FICS, FRCOG  
MUJHU Research Collaboration  
P.O. Box 23491  
Kampala, Uganda  
Phone: 256-41-4541-044  
Fax: 256-41-4532-091  
E-mail: [fmmiro@mujhu.org](mailto:fmmiro@mujhu.org)

NIAID Medical Officer  
Sheryl Zwierski, RN, CRNP  
Division of AIDS  
NIAID/NIH  
6700-B Rockledge Dr. MSC 7628  
Bethesda, MD 20892-7628  
Phone: 301-402-4032  
Fax: 301-496-8530  
Email: [szwerski@niaid.nih.gov](mailto:szwerski@niaid.nih.gov)

NICHD Medical Officer  
Lynne Mofenson, MD  
Ped, Adolescent and Maternal AIDS Branch,  
CRMC, NICHD  
6100 Executive Boulevard, Room 4B11J  
Rockville, MD 20852  
Phone: 301-435-6870  
Fax: 301-496-8678  
E-mail: [lm65d@nih.gov](mailto:lm65d@nih.gov)

Protocol Statisticians  
Tom Fleming, PhD  
FHCRC - SCHARP  
University of Washington  
Department of Biostatistics  
1959 NE Pacific, 357475  
Seattle, WA 98195  
Phone: 206-543-1044  
Fax: 206-543-3286  
E-mail: [tfleming@u.washington.edu](mailto:tfleming@u.washington.edu)

Elizabeth Brown, PhD  
SCHARP-FHCRC  
1100 Fairview Avenue North  
LE-400  
PO Box 19024  
Seattle, WA 98109  
United States  
[eliz@scharp.org](mailto:eliz@scharp.org)

HPTN Network Lab Representative and  
Protocol Virologist  
Susan Eshleman, MD, PhD  
HPTN Network Lab  
Johns Hopkins University  
720 Rutland Ave, Ross Bldg., Room 646  
Baltimore, MD 21205  
Phone: 410-614-4734  
Fax: 410-614-3548  
E-mail: [seshlem@jhmi.edu](mailto:seshlem@jhmi.edu)

Network Laboratory Quality Assurance Coordinator  
Sarah Dawson, MS, MT(ASCP)SH  
HPTN Network Lab  
International/Domestic QA/QC Coordinator  
Pathology 306B  
600 North Wolfe Street  
Baltimore, MD 21287  
Phone: 360-734-8578  
Fax: 410-614-0430  
E-mail: [sdawson7@jhmi.edu](mailto:sdawson7@jhmi.edu)

Protocol Operations Coordinators  
Lynda Emel, PhD  
FHCRC-SCHARP  
1100 Fairview Ave N., LE-400  
P.O. Box 19024  
Seattle, WA 98109-1024  
Phone: 206-667-5803  
Fax: 206-667-4812  
E-mail: [lemel@scharp.fhcrc.org](mailto:lemel@scharp.fhcrc.org)

Diana Lynn  
FHCRC-SCHARP  
1100 Fairview Ave N., LE-400  
P.O. Box 19024  
Seattle, WA 98109-1024  
Phone: 206-667-4980  
Fax: 206-667-4812  
E-mail: [dlynn@scharp.org](mailto:dlynn@scharp.org)

Protocol Pharmacist  
Scharla Estep, MS, RPh  
Pharmaceutical Affairs Branch  
Division of AIDS/NIAID/NIH  
6700B Rockledge Drive, MSC 7620  
Bethesda, MD 20892-7620  
Phone: 301-435-3746  
Fax: 301-402-1506  
E-mail: [sr72v@nih.gov](mailto:sr72v@nih.gov)

Pharmaceutical Liaison  
Marita McDonough, R.N.  
Boehringer Ingelheim Pharmaceuticals, Inc.  
900 Ridgebury Road / P.O. Box 368  
Ridgefield, CT 06877-0368  
Phone: 203-798-4355  
Fax: 203-791-6269  
E-mail: [mmcdonou@rdg.boehringer-ingelheim.com](mailto:mmcdonou@rdg.boehringer-ingelheim.com)

Protocol Pharmacologist

Mark Mirochnick, MD  
Boston Medical Center  
Maternity Six  
91 E Concord St.  
Boston, MA 02118  
Phone: 617-414-3754  
Fax: 617-414-7297  
E-mail: [markm@bu.edu](mailto:markm@bu.edu)

Protocol Specialists

Kathy George, MPH  
Family Health International  
PO Box 13950  
Research Triangle Park, NC 27709  
Phone: 504-897-3001/919-405-1429  
Fax: 919-544-0207  
E-mail: [kgeorge@fhi.org](mailto:kgeorge@fhi.org)

Philip Andrew, RN  
Family Health International  
P.O. Box 13950  
Research Triangle Park, NC 27709 USA  
Phone: 919-544-7040, ext. 213  
Fax: 919-544-0207  
E-mail: [pandrew@fhi.org](mailto:pandrew@fhi.org)

## SCHEMA

### 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**

**Purpose:** To evaluate the efficacy and safety of an extended regimen of nevirapine (NVP) from 6 weeks to 6 months or through cessation of breastfeeding, whichever is earliest, for prevention of mother-to-child transmission of HIV through breast milk compared with placebo among infants who are provided nevirapine for the first 6 weeks (through Day 42) of life and are HIV-uninfected at age 6 weeks.

**Design:** Phase III, multi-site, randomized, double blind, placebo-controlled trial.

**Study Population:** HIV-1 infected women and their breastfeeding infants. As standard of care (external to the study) all HIV-infected women at the study sites are offered an antiretroviral regimen for prevention of in utero/intrapartum maternal to child HIV-1 transmission (e.g. the HIVNET 012 two-dose intrapartum/neonatal regimen of NVP). In addition, all infants enrolled in the study will receive NVP for the first 6 weeks (42 days) of life for prevention of early postnatal transmission. All infants/mothers randomized under Version 2.0 of the protocol will remain in the study and be followed for 18 months according to the study schedule. Infants enrolled under Version 2.0 of the protocol who were not randomized (including those enrolled on or after 10 August 2007) and their mothers will be followed according to the study schedule through the Month 3 visit only and will then be terminated from the study.

**Study Size:** Approximately 1670 mother/infant pairs will need to be enrolled at birth (within 7 days) in order to randomize the target of 1500 infants at six weeks. In addition, approximately 250 mother/infant pairs originally enrolled under Version 2.0 of the protocol will be followed under Version 3.0.

**Stratification:** Randomization will be stratified by maternal antiretroviral therapy with two levels based on maternal therapy for treatment of HIV at the point of randomization: mothers receiving antiretroviral therapy (ART) or mothers not receiving antiretroviral therapy (ART).

**Study Duration:** Total duration will be approximately 3.5 years. Participants will be enrolled over a period of approximately 18 to 24 months; randomized mothers and infants will be maintained in follow-up through 18 months postpartum.

#### **Treatment Regimen:**

Infants eligible under Version 3.0 of the protocol will be enrolled in the study on or before day 7 after birth:

- All infants will receive a daily regimen of open-label NVP through 6 weeks (42 days) of life starting at 3 to 7 days after birth.
- Infants still eligible at 6 weeks of age will be randomized to one of two study arms and will initiate the daily study drug regimen (NVP or NVP placebo) as outlined in the table below.

Infants enrolled under Version 2.0 of the protocol:

- Infants either randomized to the placebo arm and over 6 weeks ( $\geq 43$  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 according to the age-appropriate dose specified below.
- Infants who were not randomized (including those enrolled on or after 10 August 2007) or who were randomized to the placebo arm of the study and were under 6 weeks ( $< 43$  days) of age as of

10 August 2007 will be provided open-label NVP with dosing below through six weeks (42 days) of life.

Infants determined to be HIV-infected will be taken off of open-label NVP (if  $\leq 6$  weeks of age) or study drug (if  $> 6$  weeks (43 days) of age but will remain in follow-up as described in the protocol.

<b>Infant Dosing Regimen</b>	
<b>All enrolled infants less than 43 days of age will receive:</b>	
<b>NVP suspension (10 mg/ml) N<math>\approx</math>1670</b>	0.6 ml (6 mg) once daily from 3 to 7 days after birth to 2 weeks of age 1.5 ml (15 mg) once daily from 2 to 5 weeks of age 1.8 ml (18 mg) once daily from 5 to 6 weeks (42 days) of age
<b>Eligible infants will be randomized (N=1500) at approximately 6 weeks to receive either:</b>	
<b>NVP Suspension (10 mg/ml) (n=750)</b>	2 ml (20 mg) once daily from 6 ( $\geq 43$ days of age) to 8 weeks of age 2.2 ml (22 mg) once daily from 8 weeks to 3 months of age 2.4 ml (24 mg) once daily from 3 to 4 months of age 2.6 ml (26 mg) once daily from 4 to 5 months of age 2.8 ml (28 mg) once daily from 5 to 6 months of age
<b>NVP Placebo (n=750)</b>	2 ml once daily from 6 to 8 weeks of age 2.2 ml once daily from 8 weeks to 3 months of age 2.4 ml once daily from 3 to 4 months of age 2.6 ml once daily from 4 to 5 months of age 2.8 ml once daily from 5 to 6 months of age

*Note:* Local standard of care antiretroviral regimen for prevention of *in utero*/intrapartum mother to infant HIV transmission will be offered to all mothers and infants (outside of the study) regardless of their participation in HPTN 046.

*Note:* Infants will be considered to be the appropriate age for dose adjustment if they are no more than one week below the target age, except at two and six weeks of age. Infants will be eligible for the two week dose adjustment at only two days prior to the target age of two weeks. Randomized infants will begin the six week dose adjustment at  $\geq 43$  days of age.

### Study Objectives:

The primary objectives of this study are to:

1. Compare the rate of HIV infection at 6 months in infants determined to be HIV uninfected at 6 weeks in each arm.
2. Evaluate and compare the safety and tolerance in infants in each arm.

The secondary objectives of this study are to:

1. Compare the proportion of infants who are alive and free of HIV at 6 months and 18 months of age in the two arms.
2. Compare the relative rates of HIV infection in infants over 18 months in the two arms.
3. Compare the infant survival rates (mortality regardless of HIV infection) over 18 months in the two arms.
4. Determine the frequency and duration of NVP-resistant HIV strains in maternal plasma and breast milk and the relationship with MTCT.

5. Determine the relationship of maternal plasma and breast milk RNA levels to risk of MTCT.
6. Determine the frequency, type, and duration of NVP-resistant HIV strains in the plasma of infants who become HIV-infected.
7. Compare the rates of HIV disease progression, as defined by CD4+ cell count, HIV-1 RNA copy number, and mortality between the two arms in infants who become HIV-infected.
8. Determine NVP concentrations in infants who become infected with HIV and a sample of HIV uninfected infants as an index of adherence to the NVP regimen.

**Study Sites:** The study will be conducted at the following locations and/or other DAIDS Clinical Trials Sites:

- Prince Mshiyeni Hospital; Durban, South Africa
- Muhimbili Hospital; Dar es Salaam, Tanzania
- Mulago Hospital; Kampala, Uganda
- Chitungwiza Clinics; Chitungwiza, Zimbabwe

## 1.0 INTRODUCTION AND BACKGROUND

In 2006, an estimated 530,000 children became infected with HIV, mainly in developing countries. Since the beginning of the HIV epidemic, an estimated 2.3 million children worldwide have been infected with HIV. Mother to child HIV transmission (MTCT) is responsible for more than 90% of these infections, in which HIV is transmitted during pregnancy, labor, delivery, or during breastfeeding. Among infected infants who are not breastfed, about two-thirds of the cases of MTCT occur around the time of delivery and the rest during pregnancy (mostly during the last 2 months) (1). In populations where breastfeeding is the norm, postnatal transmission through breast milk accounts for more than one-third of all transmission (2-6). Therefore, even though antepartum and intrapartum antiretroviral regimens have been shown to significantly reduce MTCT, these substantial gains may be lost in breastfeeding populations in which infants have continued exposure to HIV through breast milk.

In most developing countries, where the majority of MTCT continues to take place, promotion of breastfeeding has been central to maternal and child health and to reducing infant mortality by providing optimal nutrition, by protecting against common childhood diseases, such as diarrheal and respiratory infections, and by promoting child spacing (7,8). However, HIV infection is also transmitted through breast milk, leading to the dilemma that replacement feeding, while protecting against HIV infection, may also place the infant at greater risk of dying from other infections (9). This is particularly true in rural areas and regions where limited access to clean water increases the risk of diarrheal disease if replacement feeding is used. Additionally, the societal norm in most developing countries is breastfeeding, and there are extraordinary social and family pressures to breastfeed. The use of formula feeding may be viewed as a surrogate for HIV infection and lead to social stigmatization, discrimination, and even violence and abandonment of the woman and her infant. Concerns for confidentiality may significantly influence a woman's decision to breastfeed (10). Thus, the universal promotion of formula feeding as an alternative to breastfeeding for HIV-infected women in developing countries is often not a feasible or even desirable option. Even in those areas where an HIV-infected mother might have the choice to use formula, the decision to breastfeed appears to be influenced by considerations such as the cost of formula, fear of disclosure of HIV status, and cultural constraints. 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.

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.

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 or 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 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.

## **1.1 Breastfeeding and Mother to Child Transmission**

### **1.1.1 Benefits of Breastfeeding**

The many advantages of breastfeeding have been well documented. The practice is known to confer health, nutritional, immunological, developmental, psychological, social, and economic benefits (7,8,12).

Studies have shown that breastfeeding provides general health, growth, and development benefits to the infant, while significantly decreasing the risk of a number of acute and chronic diseases. Breast milk provides secretory antibodies against specific pathogens as well as non-specific broad-spectrum protection from pathogens by milk constituents such as leukocytes, fatty acids, lactoferrin, glycoconjugates (such as lactadherin and oligosaccharides), nucleotides, immunomodulators, and anti-inflammatory agents (13). Breastfeeding has an important role in regulation of the immune response during infancy and has been shown to lower infant morbidity and mortality and decrease the incidence and/or severity of gastrointestinal and lower respiratory tract infections, otitis media, and necrotizing enterocolitis (12,14-16). These benefits are greatest among infants who exclusively breastfeed; exclusively breastfed infants are less likely than mixed breastfed infants to have diarrheal or respiratory illness or to develop atopic disease (7,17).

In a meta-analysis, breastfeeding was associated with a six-fold (95% confidence interval [CI] 6-10) decrease in mortality due to infectious diseases for infants less than 2 months of age. Protection persisted but declined with age during infancy with a four-fold (95% CI 3-6) decrease for ages 2 to 3 months, a three-fold (95% CI 2-4) decrease for ages 4 to 5 months, a two-fold (95% CI 1-3) for ages 6 to 8 months and 1.4-fold (95% CI 1-3) for ages 9 to 11 months (16). Others have similarly shown that the protective effects of breastfeeding are greatest in the first 6 months of life (18,19). Breast milk contains

carbohydrates, fats, amino acids, minerals and vitamins as well as various growth-promoting factors, enzymes, hormones and substances such as epidermal growth factor, insulin and somatomedin and provides optimal nutrition to infants, particularly during the first 12 months of life (18,20).

Breastfeeding also provides benefits to the mother. Breastfeeding delays resumption of ovulation resulting in increased child spacing. There are also psychosocial benefits of breastfeeding through promotion of maternal-infant bonding. In addition to individual health benefits, there are economic and social benefits due to savings for formula purchases for the child and decreased health care costs due to lowered rates of infant disease.

Nduati and colleagues have reported a post-hoc observation that maternal deaths were increased over 24 months in infected mothers who breastfed compared to those who fed with formula, with cumulative mortality 10.5% vs. 3.8%, respectively (21). It was hypothesized that the increased metabolic demands of breastfeeding in a population with already marginal nutritional status secondary to HIV infection could result in substantial nutritional impairment and wasting. However, a vitamin A intervention study from Durban, South Africa, did not detect any significant effect of breastfeeding on maternal morbidity, maternal deaths, CD4+ cell counts, or hemoglobin (22).

#### 1.1.2 HIV Transmission through Breastfeeding.

A large number of studies have provided definitive evidence that HIV is transmitted through breast milk; these data have been reviewed in depth in several recent papers and will not be discussed here (9,17,23).

A meta-analysis of data from five studies found the overall additional risk of MTCT attributed to breastfeeding from chronically infected women to be 14% (95% CI: 7-22%) (24). A prospective study in South Africa reinforces these results with the estimated rate of breastfeeding transmission being 12% by 15 months of age (22). In a randomized trial of formula vs. breastfeeding in Kenya, the cumulative probability of HIV-1 infection at 24 months was 36.7% (95% CI: 29-44%) in the breastfeeding arm and 20.5% (95% CI: 14-27%) in the formula arm; the estimated rate of breastfeeding transmission at 24 months was 16.2% (95% CI: 6.5%-25.9%) (6). Transmission of HIV through breast milk accounted for 44% of overall HIV transmission in this study.

While data show a correlation of duration of breastfeeding with transmission, the risk of HIV transmission over time while breastfeeding has been difficult to determine, in part due to the difficulty in distinguishing between intrapartum and early breast milk HIV transmission and to methodological differences in studies. In a meta-analysis based on four cohorts in Africa, Leroy and colleagues found a risk of breast milk transmission (defined as transmission occurring after 2.5 months of age) of 3.2 per 100 child years of breastfeeding (3). In a prospective cohort study in Malawi that evaluated breast milk transmission starting at an earlier time point (transmission occurring after 1 month of age), Miotti and colleagues reported a relatively high risk of HIV transmission, 0.7% per month, from early breastfeeding between ages 1-5 months and 0.6% per month between 6-12 months, with a lower but continuous risk from late breastfeeding transmission (0.3% incidence per month from 12-17 months) (4). The overall rate of breastfeeding transmission in the meta-analysis was less than half that observed in the Malawi study (3.2 vs. 6.9 per 100 person years, respectively) with the greatest difference in reported

transmission being in the first 1-5 months (3.5% in Malawi compared with 0.7% in the meta-analysis). These differences may be due to different definitions of postnatal transmission, with the Malawi study including earlier time points that were associated with the highest rates of transmission. Consistent with the Miotti study, data from two randomized clinical trials (the Kenya and SAINT trials) also suggest that breastfeeding transmission is highest in the first 2 months of feeding. In the Kenya study, the breastfeeding group had 6.3% more infections between delivery and 6-8 weeks than the formula fed group; similarly, in the SAINT trial in South Africa (described in Section 1.3.2), there were 5.6% more new HIV infections among breastfed infants in the same time period (6,25).

In addition to duration of breastfeeding, other risk factors for breastfeeding transmission include maternal viral load, cell-free virus in breast milk, breast pathology (mastitis, breast abscess, cracked nipples), and infant thrush before age 6 months (26-28). Sub-clinical mastitis may also increase the risk of breastfeeding transmission (27,29). A few observational studies have found that exclusive breastfeeding may be safer than mixed breastfeeding (30,31). However, this finding requires further investigation.

### 1.1.3 Data from Infant Prophylaxis Trials

#### 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

In July 2003, results of the SIMBA (Stopping Infection from Mother-to-Child from Breastfeeding in Africa) study were presented at the International AIDS Society (IAS) Meeting, Paris, France (32). 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 (AZT) and didanosine (ddI) from 36 weeks of pregnancy, intrapartum, and for 1 week postpartum. Infants were randomized to NVP (N=198) vs. 3TC (N=199) throughout breastfeeding and for 1 month after cessation. Overall, 43 of 397 (11%) infants had HIV infection or died by age 6 months. In Kaplan-Meier analyses, the overall rate of HIV infection was 8% (95% CI, 5-10%) and the overall rate of either HIV-infection or death was 10% (95% CI, 7-12%). Excluding infants positive at birth, 3 of 367 (0.8%) infants became infected between birth and age 4 weeks, and another 3 of 358 (0.8%) became infected between 4 weeks and 6 months (2/179 [1.1%] on 3TC, and 1/179 [0.6%] on NVP), for a total of 1.6% infected following birth (comparison between 3TC and NVP was not statistically significant).

The preliminary report from this Phase II trial and its relevance to the HPTN 046 design have been carefully considered by the HPTN 046 team as well as by the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine and Prevention DSMB. The 12-15% late postnatal transmission reported in most prior studies was in the context of ongoing breastfeeding into the second year of life whereas the median length of breast feeding in SIMBA was only about 3 months. In addition, critical covariates for HIV transmission such as maternal viral load at delivery (median RNA = 2.74 log copies/mL) were substantially different from those in other African studies. SIMBA used a background of maternal AZT/ddI treatment during pregnancy, intrapartum, and one week postpartum in the mothers, whereas most perinatal studies and most governmental programs implementing MTCT prevention programs in the international arena are using the HIVNET 012 two-dose intrapartum/neonatal NVP regimen. The SIMBA regimen is more complex and is therefore unlikely to be implemented as national policy in Tanzania, Zimbabwe, South Africa or Uganda at this time. The duration of breastfeeding reported in SIMBA was 3.3-3.5 months. Thus, breastfeeding and risk of transmission ceased on average approximately 2.5 months before the 6-month study endpoint. In contrast, the median duration of breastfeeding in HIVNET 012 conducted in Uganda was 9 months. Additionally, since there was such early weaning in SIMBA, it will be critical to also evaluate infant growth and morbidity data in SIMBA participants to adequately address

the risk of the intervention. The percentage of exclusive breastfeeding is much higher in SIMBA (>90%) than seen in other breastfeeding studies. Whether this intervention without any antiretroviral prophylaxis would also lower the risk of breast milk HIV transmission is controversial, but some researchers believe exclusive breastfeeding lowers risk. An important covariate in the risk of postnatal transmission is maternal RNA at delivery. The median reported RNA in the NVP arm in SIMBA was 2.74 (IQR 2.6-3.5) log, compared with 4.4 log in HIVNET 012. Plasma RNA levels have been shown in several studies to be an important determinant of breast milk transmission and to correlate with breast milk viral load. Consider the subgroup of HIVNET 012 women who had HIV RNA less than the median level of 4.4 log copies/mL. 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 antiretrovirals, (assuming AZT/ddI leads to a 1.1 decrease in log HIV RNA). In this group from HIVNET 012, the postnatal rate of infant infection was only 1.4%.

Thus, while the preliminary results from this Phase II trial are encouraging, the HPTN 046 team as well as the NIAID DSMB concluded that available SIMBA data are too limited to make any formal conclusions. The SIMBA study did not include a control arm in which no infant prophylaxis was provided, therefore it is not possible to differentiate whether the observed rate of breast milk transmission is due to the AZT/ddI treatment of the mother, which included postnatal therapy; the low viral load in the mothers at delivery; the short duration of breastfeeding; or other factors. This Phase II study does not conclusively demonstrate the efficacy of infant prophylaxis in reducing breast milk transmission, nor are the regimens currently applicable to a broad population of breastfeeding women, such as late presenting women who could not be offered prenatal antiretroviral interventions.

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 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 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).

Like SIMBA, the lack of a control group (e.g., a group of infants breastfeeding without 6 month infant AZT prophylaxis) in the Mashu study makes the data inadequate to accurately assess the potential efficacy of 6 month infant prophylaxis of postnatal transmission. However, in the Mashu study, 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. Additionally, the Mashu data suggest the importance of identifying ways to safely breastfeed, given the higher infant mortality with formula feeding.

The SIMBA and MITRA studies 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.

#### 1.1.4 Breastfeeding in Developing Countries in Africa

Breastfeeding is the norm in the countries in which this study will be conducted. A representative national study in South Africa on childhood nutrition found that 88% of mothers initiated breastfeeding and that 95% of those mothers continued breastfeeding for at least 3-5 months. In Zimbabwe, 98.7% of mothers initiated breastfeeding; at 6-7 months, only 0.8% had weaned their infants. In a study conducted in Dar es Salaam, Tanzania, 90% of women were still breastfeeding at 3 months and 87% at 6 months. In recent studies of antiretrovirals to reduce MTCT in West and East Africa and KwaZulu Natal, South Africa, the overwhelming majority of HIV-infected women chose to breastfeed their babies despite receiving counseling on the risks and benefits of breast and formula-feeding. In the HIVNET 012 trial in Uganda (described in Section 1.3.2), 99% of women breastfed their infants; 80% were still breastfeeding at 6 months and 12% were still breastfeeding at 18 months (39,40). In the SAINT trial in South Africa (described in Section 1.3.2), 43% of infants were breastfed, with 75% still breastfeeding until 3 months, 11% until 6 months and 14% until 1 year (25).

Adherence to formula feeding in populations where breastfeeding is the norm may be problematic. For example, in the trial of breastfeeding versus formula feeding of infants born to HIV-infected women in Kenya, in which women were provided with considerable support to initiate and maintain formula feeding, more than 25% of those randomized to the formula feeding group were reported to have also breastfed their infants (6). The Kenya trial revealed the difficulties of balancing risks between breast and formula-feeding for HIV-infected women in developing countries. Infant mortality at 24 months was similar for the formula-fed and breastfeeding groups, despite a 40% lower risk of HIV transmission in the formula fed group. Furthermore, the morbidity and mortality during the first few months of life were higher in the formula group; this applied to both HIV-infected and HIV-uninfected infants. The cost to HIV-exposed but uninfected infants is therefore a serious consideration in policies on breast versus replacement feeding in poor populations.

Current World Health Organization (WHO) recommendations emphasize that breastfeeding should continue to be supported and promoted in all populations, irrespective of HIV infection rates; that there should be improved access to HIV counseling and testing; and that HIV-infected women should be fully counseled about the



benefits of breastfeeding, the risk of HIV transmission through breastfeeding, and the risks and possible advantages associated with other methods of infant feeding; and should be supported in their choice of infant feeding (41).

## 1.2 Rationale for Extended Regimen of NVP to Prevent MTCT

Given the many advantages of breastfeeding, the significant obstacles to substituting formula for breast milk in developing countries, and the documented risk of HIV transmission through breastfeeding, there is an urgent need to make breastfeeding by HIV-infected women safe from transmission of the virus to their infants. 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 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.

NVP was selected for evaluation as the antiretroviral drug candidate for prevention of vertical HIV transmission based on its relatively long half-life, excellent bioavailability, potent antiretroviral activity, ability to be administered in a once-daily dosing regimen, established safety with single dose neonatal administration in over 1,600 mother-infant pairs, and established safety when used in multiple doses for treatment of infected children (42,43).

NVP is a non-nucleoside reverse transcriptase inhibitor (NNRTI). It is structurally a member of the dipyridodiazepinone chemical class of compounds and is a potent inhibitor of HIV-1 replication with an inhibitory concentration (IC)<sub>50</sub> of 10 ng/ml. It has excellent oral absorption and bioavailability, and a high therapeutic index. NVP is highly lipophilic and widely distributed throughout the body, and has been shown to penetrate cell-free HIV-1 and inactivate virion-associated reverse transcriptase *in situ*. NVP prophylaxis has been shown to prevent infection in chimpanzees challenged with HIV-1 (44). It has been well tolerated when used therapeutically in HIV-infected adults, children, infants, and as a single dose in the first week of life for prophylaxis of MTCT in HIV-exposed neonates (39,42). The main route of NVP elimination is hepatic, with metabolism by the liver cytochrome p450 metabolic enzymes (primarily CYP3A4 and CYP2B6, and to a lesser extent, CYP2D6 and CYP2C9). It is an inducer of hepatic cytochrome p450, resulting in an “autoinduction” phenomenon characterized by an approximately 1.5 to 2-fold increase in apparent oral clearance and decrease in terminal half-life after 2-4 weeks of daily dosing in children and adults (45).

### 1.2.1 Rationale for NVP Resistance Testing

Resistance with monotherapy is a concern. The rate of NVP resistance in women and infants receiving NVP prophylaxis in this trial could be higher or lower than that observed in HIVNET 012 (described in Section 1.3.2). HIV-infected children in this trial are likely to receive NVP before their infection is discovered. This provides an opportunity for *de novo* selection of NVP resistance in infants infected at birth or post-partum. NVP-resistant HIV could also be transmitted to infants via breastfeeding. Prolonged use of NVP in the post-partum period could further increase the rate of NVP resistance in infants who are infected at birth or post-partum. The types of mutations that arise in infants receiving 6 months of NVP and the rate at which NVP-resistant HIV fades in women and infants in this trial may also differ from findings in HIVNET 012.

It is important to assess if NVP resistance has an effect on the efficacy of NVP prophylactic regimens. First, if NVP-resistant virus is selected in a mother, it may

increase the probability that a breastfeeding infant would be infected despite NVP prophylaxis. Second, selection of resistant virus may affect the utility of NVP prophylaxis in a subsequent pregnancy. Third, selection of resistant virus in women could lead to transmission of NVP resistant HIV to the community. Fourth, as discussed above, it is probable that some children will become HIV infected while continuing to receive NVP but before their HIV status is determined. Finally, emergence of NVP resistance in women or infants receiving NVP prophylaxis could also limit their future options for antiretroviral treatment. These issues emphasize the importance of resistance testing in this cohort.

There is currently no evidence that NVP resistance influences the health of women or infants. However, in HIVNET 012 (described in Section 1.3.2) it was not possible to address those issues because the number of HIV-infected infants was small, and women were followed systematically for only 6 weeks after delivery. The larger size of this cohort, extended duration of the infant regimen and longer follow-up of women and infants may offer an opportunity to address these important issues.

### **1.3 Intrapartum/Neonatal NVP for Reducing Intrapartum MTCT**

#### **1.3.1 Pharmacokinetics of Intrapartum/Neonatal NVP**

Prophylactic use of NVP has targeted achievement of drug levels of 100 ng/ml, which is 10 times the *in vitro* IC<sub>50</sub> of the drug for HIV. It is likely that lower NVP concentrations are required to prevent infection than to treat established infection. However, no data are available that indicate the NVP drug concentration required to prevent transmission.

The pharmacokinetics of NVP following initial dosing during the third trimester are similar to those in non-pregnant adults (46). In Pediatric AIDS Clinical Trials Group (PACTG) 250, done in the U.S., NVP elimination was found to be prolonged when administered to pregnant women during labor, with the half-life increasing from 43 hours during the third trimester to 73 hours during labor. NVP crossed the placenta readily, and the ratio of cord blood to maternal NVP blood concentration averaged approximately 80%. Because of immature liver metabolism, the half-life of NVP in neonates was prolonged compared to older children; the half-life of a single dose of NVP administered at age 48-72 hours in neonates was 36.8 hours (range 27.3-49.5 hours) (46). A pharmacokinetic study in African pregnant HIV-infected women and their infants studied in Uganda (HIVNET 006) yielded similar results (47). As a result of the rapid absorption and distribution of NVP and its relatively slow elimination in women in labor and newborns, administration of a single 200 mg dose of NVP during labor and a single dose of 2 mg/kg to the infant at 48-72 hours after birth maintains NVP concentrations in the infant above 100 ng/ml (10 times the *in vitro* IC<sub>50</sub>) throughout the first week of life; this regimen was shown in HIVNET 012 (described below) to significantly decrease MTCT (39).

#### **1.3.2 Efficacy of Intrapartum/Neonatal NVP for Preventing MTCT**

The efficacy of NVP in reducing MTCT of HIV during labor and delivery was evaluated in three Phase III efficacy trials: HIVNET 012 (in Uganda); SAINT (in South Africa); and PACTG 316 (in the U.S., Europe, Bahamas and Brazil). These studies are described below.

HIVNET 012 was a perinatal trial in breastfeeding women in Uganda that compared two intrapartum/neonatal regimens: a NVP regimen consisting of a single 200 mg dose of oral NVP to the mother at the onset of labor and a single 2 mg/kg dose of NVP to the infant within 72 hours of life, and an ultra-short AZT regimen consisting of 600 mg orally to the mother at the onset of labor and 300 mg every 3 hours until delivery and 4 mg/kg orally twice daily to the infant for 7 days after birth (39). The study enrolled 626 HIV-infected pregnant women and their infants, 313 in the NVP and 313 in the AZT group. The NVP regimen was found to reduce the risk of HIV-1 transmission by 47% (95% CI: 20-64%) at 14-16 weeks compared to the AZT regimen. The estimated risks of MTCT in the NVP and AZT groups were 8.2% and 10.4% at birth; 11.9% and 21.3% by age 6-8 weeks; and 13.1% and 25.1% by age 14-16 weeks, respectively. Follow-up has been reported through age 12 and 18 months (40,48). At 18 months, transmission was 15.7% in the NVP group compared to 25.8% in the AZT group. Thus, NVP efficacy was maintained through 18 months of age, with an estimated efficacy of 41% (95% CI: 16-59%). However, postpartum MTCT through breastfeeding continued to occur in both treatment groups. Almost one-quarter of all infant infections in the NVP group (an absolute rate of 4%) occurred postnatally between 6-8 weeks and 18 months of age.

The SAINT study, conducted in South Africa, compared a modified HIVNET 012 NVP regimen (a single 200 mg dose of NVP given to the mother at onset of labor, another 200 mg dose to the mother 24-48 hours after delivery, and a single 6 mg dose given to the infant 24-48 hours after delivery) to a combination intrapartum/postpartum AZT and lamivudine (3TC) regimen (given orally to the mother at onset and during labor and for 7 days to the mother and infant) that had been shown to be effective in reducing mother-to-child transmission in the PETRA study (25,49). Breast- and formula-fed infants at 11 sites in South Africa were tested for HIV-1 at birth, 4 weeks and 6 to 8 weeks by DNA PCR. A total of 1318 women and 1330 infants were randomized. The overall estimated HIV infection rates by eight weeks in 1307 infants (654 NVP, 653 AZT/3TC) were 12.3% (95% CI: 9.6-15.0) in the NVP group and 9.3% (95%CI: 7.0-11.7) in the AZT/3TC group. Excluding infections detected within 72 hours of birth, which reflect *in utero* transmission (50), 5.7% (95%CI: 3.6-7.7) of infants in the NVP group and 3.6% (95%CI: 2.0-5.2) in the AZT/3TC group were infected within 8 weeks after birth. Maternal viral load, CD4+ cell count, timing of maternal dose, prolonged rupture of membranes were risk factors for infant infection. Infection-free survival rates at 8 weeks were 85.9% (95%CI: 82.8-89.1) in the NVP and 87.7% (95%CI: 84.9-90.5) in the AZT/3TC group. Thus, a comparison of two short-course intrapartum/neonatal antiretroviral regimens showed both were similarly effective.

PACTG 316 was a randomized, double-blind, placebo-controlled trial conducted in the U.S., Europe, Bahamas and Brazil, designed to evaluate the safety and efficacy of intrapartum/postpartum NVP compared to NVP placebo added to standard antiretroviral therapy for the prevention of MTCT (51). HIV-infected pregnant women receiving standard antiretroviral therapy were randomized to receive 200 mg NVP or NVP placebo during active labor; infants received 2 mg/kg NVP or placebo at 48-72 hours. Seventy-seven percent of women received combination therapy (28% AZT/3TC, 8% other combinations without and 41% combinations with protease inhibitors) and 23% received AZT monotherapy as per the PACTG 076 regimen; infants received the 6-week AZT PACTG 076 prophylaxis regimen. Thirty-four percent of women had elective cesarean delivery. Twelve hundred and seventy mother-infant pairs received study drug (642 in the NVP group) and had infection status known. No infant was breastfed. Overall transmission was 1.4%, with 1.4% in the NVP arm and 1.5% in the placebo group; 56%

of the infected infants were infected *in utero*. The study was discontinued prior to full accrual because the perinatal transmission rate was significantly lower than expected and the planned sample size was not sufficient to meet the primary objective of the study. Thus, among HIV-infected women who had adequate prenatal care, were treated with standard antiretroviral antenatal therapy (generally combination ART), did not breastfeed, and for whom elective cesarean section was a safe option, the risk of perinatal transmission was very low and administration of the 2-dose intrapartum/neonatal NVP regimen did not produce a clinically relevant further lowering of transmission.

### 1.3.3 Safety of Intrapartum/Neonatal NVP

Safety data on the NVP maternal intrapartum/neonatal regimen are available from two Phase I studies, PACTG 250 and HIVNET 006, and the three Phase III studies discussed above.

PACTG 250 was a Phase I safety and pharmacokinetic study of the intrapartum/neonatal NVP regimen in women and infants in the U.S (46). PACTG 250 enrolled 17 HIV-infected pregnant women and their babies. No clinical or laboratory toxicities related to NVP were observed in either mothers or babies, and no severe rashes were noted.

This Phase I study was repeated in 21 Ugandan HIV-infected women and their infants in the HIVNET 006 study (47). No serious adverse experiences or grade 3 or 4 clinical or laboratory toxicities related to NVP were seen in the mothers. There was one serious adverse experience in an infant thought by the investigators to be possibly, but not likely related to study drug. This was an infant who developed respiratory distress at birth and seizures after a difficult and prolonged labor requiring forceps. No other serious adverse experiences that were attributable to study drug were observed in the infants and no women or infants had rash toxicity.

In the HIVNET 012 trial in Uganda (described in Section 1.3.2), 313 HIV-infected pregnant women and their infants received NVP (39). Complete blood cell count (CBC) and chemistries were monitored in the infants at age 24 hours, 7 days and 6 weeks. Mothers had a CBC at 24-48 hours postpartum and chemistries done at 7 days postpartum. The rates of maternal serious adverse experiences were similar between the NVP and AZT groups (4.7% and 4.4%, respectively) and the occurrence of clinical and laboratory abnormalities were again similar in both groups. Nine women (4 in the AZT and 5 in the NVP group) had maculopapular rash but none were serious. Reported serious adverse experiences among infants within 56 days of birth were balanced between the two groups (12.3% in the AZT group and 10.9 % in the NVP group). Of the 64 babies with at least one serious adverse experience reported within 56 days of birth, seven (2.3%) in the AZT group and two (0.6%) in the NVP group were thought to be possibly but unlikely due to study drug. In the two NVP group infants, these adverse experiences were transient respiratory distress at birth with meconium staining requiring oxygen, and a non-macerated stillbirth to a mother who had received NVP 3.5 hours before delivery. Eighteen babies, balanced between the two groups had maculopapular rash, no case of which was serious. The frequency and severity of laboratory adverse effects were similar between the two AZT and NVP arms as well (including hematologic and chemistry abnormalities). Reports of serious adverse experiences through 18 months of follow-up were also balanced between the two groups (40). There were 76 deaths among 629 babies in follow-up through 18 months, 13.6 % in the AZT group and 10.6% in the NVP group. The most frequent cause of death was pneumonia, followed by

gastroenteritis/diarrhea/dehydration, anemia, and malaria. NVP was associated with significantly longer HIV-1 free survival at 18 months. When stratified by babies' infection status at age 6-8 weeks, survival rates at 18 months were similar in both groups. In the SAINT study in South Africa (described in Section 1.3.2), there was no difference in the frequency of maternal serious or non-serious adverse experiences or deaths between women receiving AZT/3TC or a modified HIVNET 012 NVP regimen described above. (52). The most common maternal adverse experiences through 28 days post-delivery were related to obstetrical procedures (23.7% in NVP group; 26.4% in AZT/3TC group;  $p = 0.25$ ). The rate of rash was similar in both arms. Nine women died in the study: 5 in the NVP arm and 4 in the AZT/3TC arm. None of these deaths were considered to be treatment related. Twelve (9%) infants weighing less than 2 kilograms at birth received study medication. The non-serious adverse experiences reported for infants through 28 days of life were also similar in both treatment groups and most were respiratory system disorders. There was no difference in the occurrence of rash in the two groups of infants. The rates of serious adverse experiences (clinical or laboratory abnormalities) were similar in the two treatment groups, 8.5% in the NVP and 9.8% in the AZT/3TC group. The most frequent serious adverse experiences were respiratory system disorders (NVP 3.8%, AZT/3TC 4.2%) and infections (NVP 2.3%, AZT/3TC 3.0%). There were 13 infant deaths in the NVP arm; 10 of which were related to HIV infection, 5 to gastroenteritis, 3 to pneumonia and 1 to birth asphyxia. None of the deaths was related to drug toxicity.

In PACTG 316 (described in Section 1.3.2), the toxicity monitoring included a CBC and SGPT in the mothers at delivery and 4-6 weeks postpartum and in the infant at birth, 6-9 days and 4-6 weeks of life. Overall, significant toxicity was rare in both mothers and infants and did not differ between NVP and placebo groups (51). Only two women had a severe (grade 3 or higher) rash after study drug, one in each treatment group. Non-rash serious toxicity (grade 3 or higher) after study drug was rare and similar in both arms (6% in each treatment group). Grade 3 or higher hepatic toxicity (elevated alanine aminotransferase (ALT) or bilirubin) was reported in 10 women, 5 in each treatment group (4 women, 2 per group, with known underlying liver disease). Three women died during postpartum follow-up (2 NVP, 1 placebo); none of the causes was attributed to study drug (ischemic cardiomyopathy; sickle cell disease, and disseminated histoplasmosis). Four infants (1 NVP, 3 placebo) had a reported grade 3 or higher rash, 2 between birth and 3 days and 2 at  $\geq 4$  days of age; no rash was attributable to NVP. Serious non-rash toxicity (grade 3 or higher) was observed in 30% of infants, and was similar between the two treatment arms; most were judged unrelated to study drug. The most frequent experiences included anemia (13%) and neutropenia (13%). Three infants (2 NVP and 1 placebo) had grade 3 or higher hepatic toxicity. All 3 were attributed to cytomegalovirus infection with hepatitis. Eight infants died (3 NVP, 5 placebo); deaths were due to SIDS (3), bacterial infection (2), post-operative gastric hemorrhage (1), trauma (1) and unknown (1) and none were attributable to study drug.

#### 1.3.4 NVP Resistance with the Intrapartum/Neonatal NVP regimen

High-level NVP resistance can be induced by a single point mutation in the HIV reverse transcriptase coding region (K103N or Y181C). HIV variants with these mutations are present at low background levels in HIV-infected individuals prior to NVP exposure (53). Exposure to NVP in the presence of replicating virus rapidly selects for these pre-existing NVP-resistant variants, which may become the major quasispecies as replication of NVP-

sensitive virus is inhibited. NVP resistance is seen within 4 weeks in almost all patients receiving NVP monotherapy (54).

Emergence of NVP resistance after single dose NVP prophylaxis was first reported in 3/15 (20%) of women in the Phase I/II Ugandan HIVNET 006 trial (55). In that study, detection of NVP resistance 6-8 weeks after single dose NVP was associated with a longer median NVP elimination half-life, decreased median oral clearance, and increased median area under the concentration time curve.

The emergence and fading of NVP resistance was further evaluated in women and infants in HIVNET 012, described in Section 1.3.2, (41/48 women with infected infants, 70 randomly-selected women with uninfected infants, and 33/49 infected infants) (56,57). NVP resistance mutations were detected in 19% (21/111) of women tested 6-8 weeks after delivery. The rate of NVP resistance was similar among women whose infants were and were not infected by 6-8 weeks. Development of resistance was associated with longer NVP clearance and half-life, higher maternal baseline HIV RNA and lower maternal CD4+ cell counts. Furthermore, the rate of NVP resistance was higher in women with subtype D than subtype A, suggesting that resistance rates may vary from one geographical region to another, depending on which subtypes are prevalent (58). Follow-up samples collected 12-24 months postpartum were available for 11/18 women with resistance at 6-8 weeks postpartum, and none had resistant virus detectable.

Of the 24 infected infants in the NVP group on whom specimens were available for resistance testing, 11/24 (46%) were found to have NVP resistance mutations at 6-8 weeks of age. Of the 11 infants with NVP resistance detected at 6-8 weeks, 91% were infected at birth compared to 69% without resistance. Mortality within the first year of life was similar for infants with and without NVP resistance. In infants with resistance who had follow-up samples, 4 out of 9 had no detectable resistance by 14-16 weeks of age. Among the infants who still had resistance at 14-16 weeks, 3 out of 3 tested at 12 months no longer had resistance detected. Late HIV transmission in HIVNET 012 (described in Section 1.3.2) was also evaluated. Twelve infants developed infection after 6-8 weeks of age (likely breast milk-transmitted infection; median age at diagnosis 10 months). Samples were available from 9 of these 12 infants collected 2-9 months after diagnosis; 8 out of 9 had no NVP resistance, including 2 infants whose mothers had resistant virus. One infant with NVP resistance was born to a mother who had NVP resistance detected at 6-8 weeks.

With the exception of the one infant with late infection, in those instances in which infected infants had resistant virus, the mothers either had wild type virus or virus with a different resistance mutation pattern. This suggests that the infants developed resistance *de novo* (when NVP prophylaxis was administered to an already infected infant), as opposed to resistant virus being transmitted from the mother. The one infant who developed late infection whose mother had NVP resistance detected at 6-8 weeks postpartum had the same pattern of mutations as the mother. Interestingly, the type of mutations that developed differed in women vs. infants, with K103N mutation more common in women and the Y181C mutation more common in infants. This may be relevant to future treatment, since subtype B HIV viruses with the K103N vs. Y181C mutation differ in their cross-resistance to efavirenz (59,60). Viruses with the Y181C mutation alone have little resistance to efavirenz (Y181C can enhance the level of resistance of viruses containing additional NVP mutations), whereas viruses with the K103N mutation are cross-resistant to other NNRTIs (61).

These studies demonstrate that NVP resistance can develop with single dose NVP in women and in infants who become infected despite NVP; following the single-dose of NVP without continued NVP exposure, resistance fades from detection in women and infants by 12-24 months among single dose recipients using standard genotyping methods. However, HIV with NVP resistance mutations may continue to circulate in these women and infants as minor variants, and may be maintained as provirus in infected cells. This may influence the efficacy of NVP in a subsequent pregnancy, or the efficacy of subsequent treatment of women or infants with an NNRTI-containing regimen.

Emergence of NVP resistance mutations was also analyzed in Zimbabwean women enrolled in HIVNET 023 8 weeks following administration of single dose NVP prophylaxis (62). For that study, HIV-1 genotyping was done with the TRUGENE™ HIV-1 Genotyping Kit (Visible Genetics Inc.) with modified v1.5 primers. NVP resistance mutations were detected in 8/30 (27%) women at 8 weeks following treatment with sd-NVP (2/4=50% vs. 6/26=23% of women whose infants were or were not HIV-1 infected,  $p=0.26$ ). NVP resistance mutations included K103N, V106A, Y181C, and G190A. The predominant mutation was K103N. Women in HIVNET 023 all had subtype C HIV-1. The rate of resistance among women with subtype C appeared to be similar to that observed in HIVNET 012 (described in Section 1.3.2) for women with subtype D, and higher than that observed in HIVNET 012 among women with subtype A. However, because different HIV-1 genotyping assays were used in the two trials (ViroSeq for HIVNET 012 and TRUGENE™ for HIVNET 023), the resistance rates among women in the two trials cannot be directly compared.

In PACTG 316 (described in Section 1.3.2), where all women were receiving antenatal antiretroviral therapy in addition to the single dose intrapartum study drug, resistance was analyzed in 51 NVP arm women in the U.S. with delivery RNA >400 copies/ml, 46 of whom got study drug, and 43 NPV arm women in France with delivery RNA >200 copies/ml (63, 64). NVP resistance was detected at 6 weeks postpartum in 12 of the 89 women (13%) who received single dose NVP and had some level of viral replication, despite the receipt of other antiretroviral drugs antenatally.

In the SAINT study (described in Section 1.3.2), a modified single-dose NVP regimen was given, where the women received a single dose of NVP at onset of labor and a second dose at 48 hours postpartum; their infants received a single 48 hour NVP dose. This regimen was compared to the PETRA AZT/3TC regimen, where AZT/3TC was given to women during labor and to both women and infants for 1 week postpartum. NVP resistant mutations were detected in 74 (67%) of the 111 women who received two doses of NVP. The predominant NVP mutations found were K103N (62%) and Y181C (45%). Studies of 40 infected infants [4-6 wks/age] demonstrated NVP mutations in 21 of 40 (53%). The predominant mutation was Y181C present in 53%. Paired data from 26 mother-infant pairs suggested that in a few instances NVP resistant virus may have been transmitted through breastfeeding. Long-term follow-up [9-12 months] samples were available from 57 women who were studied at 4-6 weeks postpartum. Of 36 women with NVP resistant mutations at 4-6 weeks, 28 (78%) reverted to wildtype, and eight (22%) retained NVP resistance. The K103N mutation was the most durable. No AZT or 3TC mutations were detected in the 37 women who received the multiple dose AZT/3TC regimen. Therefore, the use of a 2 dose maternal NVP regimen for prevention of MTCT is associated with a selection frequency (67%) of resistance mutations which is

3X greater than that observed with a single dose maternal regimen (19% HIVNET012). The majority of women who have NVP resistance mutations revert to wild type after 9-12 months (65).

## 1.4 Chronic Use of NVP for Treatment of HIV-Infected Children

### 1.4.1 Pharmacokinetics of NVP Treatment in HIV-Infected Infants and Children

During long-term therapy in children >2 months of age, NVP clearance is rapid, averaging ~120 ml/hr/kg in children during the first 2 years of life; subsequently there is a gradual decrease in NVP clearance, with average clearance decreasing to ~60 ml/hr/kg by age 8-10 years (42,43,66). NVP was tested in PACTG 356 in HIV-infected infants as young as age 2 weeks with a starting dose for infants age 15 days to ≤3 months of 5 mg/kg as a single daily oral dose for 14 days, increasing to 120 mg/m<sup>2</sup> twice daily for 14 days, and then to 200 mg/m<sup>2</sup> twice daily. For children aged 3 months to 2 years, the dose used is 120 mg/m<sup>2</sup> as a single oral daily dose for 14 days, and then 200 mg/m<sup>2</sup> twice daily. This dose has been well tolerated in infants. The pediatric NVP administration schedule approved for use in HIV-infected children aged 2 months up to eight years by the U.S. Food and Drug Administration (FDA) is 4 mg/kg once daily for the first 14 days, followed by 7 mg/kg twice daily thereafter. For children aged 8 years or more, the recommended dose is 4 mg/kg once daily for 2 weeks followed by 4 mg/kg twice daily thereafter. The dose of 2 mg/kg used in this protocol during the first 2 weeks of life is 40% of the initial PACTG 356 dose. The dose of 4 mg/kg used in this protocol after the first 2 weeks of life is 29% of the US FDA-approved NVP dose for HIV infected infants over age 2 months. 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.

### 1.4.2 NVP for Treatment of HIV Infection in Adults and Children

NVP has been used for treatment of HIV-infected adults and children. The drug is well tolerated and produces a rapid rise in CD4+ cell count and reduction in HIV replication. However, antiviral responses are transient when NVP is used as monotherapy, with viral levels rebounding in some individuals by 4 weeks after starting therapy due to the development of NVP resistant virus (54). In contrast, when it is administered in combination with other antiretroviral drugs, antiviral response has been profound and sustained (67). Administration of higher doses of NVP (more than 400 mg per day) in adults appears to be safe and to result in plasma levels above the IC<sub>50</sub> of resistant virus with resistant sustained antiviral responses (68,69). NVP is commonly used in combination antiretroviral regimens for treatment of HIV-infected children, including infants as young as age 2 weeks in a clinical trial (PACTG 356) (66,70,71).

### 1.4.3 Safety of NVP Used for Treatment of HIV Infection

The most frequently reported adverse experiences related to NVP are rash, fever, nausea, headache and abnormal liver function tests (42,43). 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 (72-75); 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. Increased 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 (72). 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 occurred in 0.3% of 2861 HIV-infected adult patients exposed to NVP (77). Dose escalation, using a lower “lead-in” dose of NVP for the first 2 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. In a review of the FDA voluntary adverse event reporting system, there have been 12 cases (11 in adults, one 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 (78). 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) (78). 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 (78). In a study in London of uninfected individuals receiving NVP PEP, a 20% rate of grade 3 or 4 hepatic toxicity was reported (79). 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% (43). When a two-week lower dose "lead in" period was used, the incidence of rash was decreased (66). While grade 2 or higher skin rash has been reported in up to 33% of children receiving NVP (80), serious rash is less common. In a study of 4-drug therapy including NVP (given with 2-week lead in), serious rash was observed in 6% of children (81). 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% (82). Granulocytopenia has also been reported in children receiving NVP (83); 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 (80,83). However, it should be noted the children in these studies were also receiving nucleoside analogue reverse transcriptase, such as AZT, 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 (82). 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 8 weeks through week 56, then every 12 weeks (84). 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 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 (85). 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 six 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 three infants receiving NVP (1.5%) and two 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).

#### 1.4.4 Development of NVP Resistance with NVP Used for Treatment

Viral isolates with high-level NVP resistance were obtained as early as day 14 from peripheral blood mononuclear cells of children receiving NVP monotherapy (66). Development of resistance was generally associated with rebound in viremia; however, some children had durable reduction in viral load despite the emergence of resistance.

Recent studies have indicated that mutations associated with NVP resistance result in measurable biochemical abnormalities in affected HIV variants, with the most common effect being a change in the ratio of viral RNase H to polymerase activities (86). In particular, reduced RNase H cleavage is observed. This can result in reduced replicative fitness of the resistant viral strain compared to wild type virus; this was particularly true for NVP resistant virus with the Y181C mutation. This is consistent with the theory that drug-resistant mutants rarely predominate in the absence of drug pressure because they have reduced replication fitness relative to wild-type virus. Additionally, mutations in the non-nucleoside binding pocket appear to affect the conformation of residues at the dNTP binding site and can result in a partial phenotypic reversal of multi-nucleoside resistance (87). The Y181C mutation has been shown to lead to resensitization of AZT-resistant virus to AZT treatment (87).

More detailed information regarding NVP can be found in the Investigator's Brochure and the Package Insert.

### 1.5 **HIVNET 023: Safety and Pharmacokinetics of Extended NVP Regimen**

HIVNET 023 was a Phase I/II randomized open label clinical trial to evaluate the safety and pharmacokinetics of three different NVP dosing regimens from birth to 6 months in breastfeeding infants born to HIV-infected women (85). The primary pharmacokinetic objective was to determine a NVP dosing regimen that is safe and maintains NVP plasma concentration above 100 microgram/ml continuously from birth to 6 months of life for use in a Phase III efficacy trial.

The study was conducted in general antenatal clinics in Chitungwiza, Zimbabwe and Durban, South Africa. HIV-infected women were enrolled from April 2000 to January 2001 and given an oral dose of 200 mg of NVP to administer to themselves at the onset of labor. Seventy-five of their infants (including 1 set of twins) were randomized within 48 hours of birth to 1 of 3 study arms and received either weekly, twice weekly or daily regimens of NVP from birth through 6 months of age. Infants in the weekly and twice weekly arms received 4 mg/kg/dose for the first 2 weeks of life, then 8 mg/kg/dose through 24 weeks. In the daily arm, infants received 2 mg/kg/dose for the first 2 weeks of life, followed by 4 mg/kg/dose through 24 weeks.

### 1.5.1 NVP Concentration Results

The primary NVP concentration outcome measures were trough (pre-dosing) NVP concentrations assessed in all infants. The therapeutic target was a trough concentration greater than 100 ng/ml, which is 10 times the in vitro IC<sub>50</sub> against HIV. Pre-dose (trough) concentrations were determined at 2, 8, 16, 20 and 24 weeks of age. Deficiencies in sample processing occurred at the Durban site from study initiation in April 2000 through November 2000. Inspection of the NVP concentration values and their assigned sampling times from this period reveals many sets of pre and post dose samples that are not consistent with our current understanding of NVP pharmacology. Therefore the study team decided to exclude all NVP concentration data from the Durban site from the period prior to correction of the sample processing deficiencies.

Concentrations are available for between 10 and 17 infants in each treatment arm (daily, twice-weekly and weekly) at each time point. Overall, none of the pre-dose samples from the daily dosing arm infants were below the therapeutic target of 100 ng/ml, while 3 of 65 (4.6%) of the twice-weekly samples and 48 of 75 (64%) of the weekly samples fell below the target. When all concentrations from all time points are combined for each treatment arm, median pre-dose NVP concentration was 1348 ng/ml (range: 108 - 4843 ng/ml) with daily dosing compared to 459 ng/ml (range: <25 - 1386 ng/ml) with twice-weekly dosing and 64 ng/ml (range: <25 - 1519 ng/ml) with weekly dosing. Although the twice-weekly arm maintained trough concentrations above the target concentration nearly as well as with daily dosing, the protocol team has decided to use daily dosing in this protocol, as explained below in section 1.6.

### 1.5.2 Safety Results

#### *Clinical Safety and Tolerance*

All infants enrolled at both sites are included in the clinical safety and toxicity analyses. No severe (Grade 3 or higher) skin rash, hepatic or renal toxicity related to NVP were observed. Three infants died (2 during follow-up, 1 after the 32-week visit). The causes of death included early-onset neonatal sepsis (1 infant, HIV-uninfected) and pneumonia (2, both HIV-infected with clinical evidence of AIDS). None of the deaths were attributable to study drug. The most frequent serious adverse clinical events (Grade 3 or 4 events) unrelated to study treatment were sepsis, pneumonia, meningitis, gastroenteritis, bronchiolitis, AIDS-defining conditions and congenital defects (1 polydactyly, 1 atrial septal defect). Two infants (both HIV-infected) developed hepatomegaly and 2 infants (both HIV-infected) developed splenomegaly; these events were deemed unrelated to study drug.

#### *Laboratory abnormalities*

Analysis of laboratory abnormalities was performed only for the 36 infants enrolled at the Harare site due to deficiencies in sample collection and processing present at the Durban site. The most frequent serious laboratory abnormality was neutropenia (Grade 3 or higher) noted in 8 infants. Grade 3 or higher neutropenia was reported in 4 infants in the once-weekly arm, 4 in the twice-weekly arm, and none in the daily arm. Seven of the 8 infants were asymptomatic. Faulty machine calibration at this laboratory site may have accounted for some of the reported neutropenia abnormalities. One infant had a clinical

event (presumed viral infection) temporally associated with the neutropenic episodes; the neutropenia was detected when symptoms of viral infection were noted. The neutropenia resolved in all 8 infants. In seven infants, the neutropenia was transient, and infants continued on NVP dosing through 24 weeks. In 1 infant with persistent neutropenia, the abnormality resolved after NVP was permanently discontinued. Grade 3 or higher anemia was observed in 2 infants. In both infants, anemia was judged to be possibly, but unlikely to be related to study drug. Two infants experienced Grade 3 or higher thrombocytopenia, unrelated to study drug; both infants were HIV-1-infected and the etiology was felt to be secondary to HIV infection. None of the enrolled infants had Grade 3 or higher elevations in serum ALT values. Thus, NVP was deemed safe and well tolerated by the infants in this study.

## 1.6 Rationale for Infant Daily Dosing Regimen

Based on the results of HIVNET 023 (described in the section above), the daily dosing regimen of NVP was chosen for this protocol for the following reasons. First, infants in the daily arm had fewer reported toxicities than those in either the once- or twice weekly arms. Second, based on experience with therapeutic and prophylactic drug regimens, adherence with daily dosing is likely to be better than with twice-weekly dosing. Third, consequences, in terms of maintaining consistent NVP plasma concentrations, of an occasional missed dose with the daily regimen would be negligible compared to an occasional missed dose with the twice-weekly regimen. If one dose with the twice-weekly regimen is missed, then a baby's trough level is more likely to fall below the IC<sub>50</sub> compared with missing one daily dose. Finally, the NVP trough concentrations in babies in the daily dosing arm were on average more than twice as high as those in the twice a week dosing arm. While we do not know the precise protective level, this may be very important for efficacy, as inhibitory NVP plasma concentrations must be consistently maintained during exposure.

To simplify NVP suspension dosing in HPTN 046, the level of NVP doses will be adjusted based on age rather than weight. This schedule was designed to administer an infant of average birth weight a daily dose of approximately 2 mg/kg during the first 2 weeks and 4 mg/kg thereafter. The chart below presents the NVP mg/kg doses that would be administered at the time of each HPTN 046 visit to an infant of average weight as well as the lowest weight and heaviest infant if this schedule was used in infants with the same weight distribution as those in HIVNET 012 and 023.

Age	Dose (mg)	NVP: mg/kg		
		Average weight infants NVP mg/kg	Lowest weight infant NVP mg/kg	Heaviest infant NVP mg/kg
<b>All infants will receive NVP from 3 to 7 days after birth through 6 weeks (42 days) of age.</b>				
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
<b>Eligible infants will be randomized to receive study drug (NVP or NVP placebo) from 43 days of age through 6 months of age.</b>				
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

Age	Dose (mg)	NVP: mg/kg		
		Average weight infants NVP mg/kg	Lowest weight infant NVP mg/kg	Heaviest infant NVP mg/kg
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

An infant weighing the same as an average weight infant in HIVNET 012/023 would receive a mean mg/kg NVP dose of 1.85 mg/kg (range: 1.70-2.01 mg/kg) during the first 2 weeks of life and 3.77 mg/kg (range: 3.25 to 4.26 mg/kg) from 2 weeks through 6 months of age. An infant with a weight equal to the lightest weight infant enrolled in HIVNET 012/023 would receive a mean mg/kg NVP dose of 3.05 mg/kg (range: 2.40 to 3.75 mg/kg) during the first 2 weeks of life and 5.89 mg/kg (range: 4.80 to 7.50 mg/kg) from 2 weeks through 6 months. An infant with a weight equal to the heaviest weight infant enrolled in HIVNET 012/023 would receive a mean mg/kg NVP dose of 1.28 mg/kg (range: 1.20 to 1.33 mg/kg) during the first 2 weeks of life and 2.87 mg/kg (range: 2.27 to 3.26 mg/kg) from 2 weeks through 6 months. The mg/kg NVP dose approved for treatment of 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 HPTN 046.

Use of this 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 IC<sub>50</sub> 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.

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.

## 2.0 STUDY DESIGN

This is a Phase III, multi-site, randomized, double blind, placebo-controlled trial to determine the efficacy and safety of an extended daily NVP regimen provided from 6 weeks to 6 months or through cessation of breastfeeding, whichever is earliest, compared to placebo, for prevention of MTCT in breastfeeding infants who are born to HIV-infected women, are provided a daily regimen of NVP through six weeks of age and are HIV-uninfected at age 6 weeks.

Antiretrovirals for prevention of mother to infant HIV transmission are available at all participating study sites as standard of care. The HIVNET 012 intrapartum/neonatal two-dose regimen of NVP is currently the standard of care for pMTCT; however, this may change over time and other antiretroviral regimens may be used. All pregnant HIV-infected women presenting at antenatal clinics at these sites are offered the local standard of care antiretroviral regimen for prevention mother to infant HIV transmission outside of the study.

Infants will be enrolled within 7 days after birth and initiate the open-label NVP regimen after enrollment on any day from Day 3 to 7. If infants are shown to be HIV-1 uninfected on a specimen drawn at the 5 week visit they will be randomized to one of two study arms at the six week visit. All infants enrolled in the study will receive NVP up to 6 weeks (through 42 days) of age. Infants will begin the study drug regimen, either NVP or NVP placebo, starting at age 6 weeks ( $\geq 43$  days of age) and will continue the randomized study drug regimen through 6 months of life or through cessation of breastfeeding (whichever is earliest). Cessation of breastfeeding is defined as completely stopping all exposure to breast milk for at least 30 days. Hereafter, the term “open-label NVP” refers to the initial 6 week course of NVP given to all infants and the term “study drug” refers to the regimen of NVP or NVP placebo to which infants are randomized at 6 weeks. Infants that are determined to be HIV-infected while receiving daily open-label NVP or study drug will be taken off open-label NVP or study drug but will remain in follow-up as described in protocol section 5.2.

It is anticipated that antiretroviral therapy will be available at some sites for treatment of HIV-infection during the conduct of this study. Therefore, because some women may receive antiretroviral therapy for treatment of HIV and some women may not receive treatment, randomization will be stratified by site with two levels based on maternal therapy for HIV treatment (not for PMTCT) at the point of randomization: maternal antiretroviral therapy or no maternal antiretroviral therapy.

A total of approximately 1670 breastfeeding infants born to HIV-infected eligible mothers will need to be enrolled within 7 days after birth to achieve the target of 1500 randomized at six weeks to one of the two study arms in a 1:1 ratio. Randomized infants and their mothers will be followed for 18 months postpartum. Infants who are enrolled but not randomized for any reason will be followed through 3 months postpartum.

All infants randomized under Version 2.0 of the protocol whose mothers consent for continued participation will remain in the study and be followed for 18 months according to the study schedule along with their mothers:

- those who were randomized to the placebo arm and over 6 weeks ( $\geq 43$  days) of age as of 10 August 2007 will continue the dosing regimen to which they were randomized (NVP or NVP Placebo)

- those who were randomized to the NVP arm (regardless of age) will continue the NVP dosing regimen to which they were randomized
- those who were randomized to the placebo arm and were six weeks of age or less as of 10 August 2007 were unblinded and will be provided open-label NVP through Day 42 of life.

Infants enrolled under Version 2.0 and born after 10 August 2007 were not randomized. These infants whose mothers gave consent for continued participation will be provided open label NVP through Day 42 of life. These infants and their mothers will be followed according to the study schedule through the Month 3 visit only and will then be terminated from the study.

## **2.1 Maternal Screening, Enrollment and Follow-Up**

At all study sites, as part of standard of care, pregnant women will be offered HIV counseling and testing and women determined to be HIV-infected will be provided the standard of care antiretroviral regimen for prevention of MTCT (e.g. HIVNET 012 intrapartum/neonatal two-dose NVP) outside of the study.

Also, HIV-infected pregnant women will receive general counseling on breastfeeding and safe alternatives from designated infant feeding counselors. These counselors will undergo training consistent with WHO and current local Ministry of Health (MOH) guidelines. The training will focus on providing accurate information and balanced options on infant feeding choices that are AFASS for each individual. Only HIV-infected women who, after thorough counseling, clearly wish to breastfeed will be referred to the study counselors to receive information regarding the study. Someone other than the designated infant feeding counselor will administer the informed consent process. Women who choose to breastfeed will be advised to breastfeed exclusively because this has been shown to be the optimal type of breastfeeding for child growth and development, and it is recommended by WHO, UNICEF, and UNAIDS.

Described below are the required clinical and laboratory procedures for mothers; see also Section 5 and 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 7 after birth. At screening women will undergo medical history and physical, as outlined in the Study Specific Procedures (SSP) Manual and will undergo one blood draw for CBC with differential, CD4+ cell count, stored plasma for later NVP resistance, HIV-1 RNA PCR testing. Women that are screened prior to labor and delivery will repeat the clinical and laboratory procedures at labor and delivery (on or before Day 7 post delivery). Post-delivery, enrolled mothers will be seen at 2 and 6 weeks and 3, 6, 12, and 18 months. Medical history and physical examinations, as outlined in the SSP manual, will be conducted at every follow-up visit. Maternal blood for CBC with differential, CD4+ cell count, and plasma storage for NVP resistance and HIV-1 RNA PCR testing will be drawn at 2 and 6 weeks and 3, 6 and 12 months. At 18 months, a plasma sample will be stored for NVP resistance testing. Dried blood spots will be stored, for back-up testing, at each maternal visit.

Weaning will be encouraged at 6 months; however, the timing of breastfeeding cessation will be determined by the mother and is likely to depend on a number of economic and social factors. Independent counselors that are not involved directly with the study procedures will be available to women throughout the study to offer continuous support on the feeding choice to the women. Throughout the study, breastfeeding status and practices will be assessed by interview. Breast milk will be collected and stored at 2 and 6 weeks and 3, 6 and 12 months. The breast milk sample will only be collected from women who are still breastfeeding at each time point, despite



counseling regarding early cessation of breastfeeding at 6 months. These samples may be tested at a later date for NVP resistance and HIV-1 RNA PCR copy number.

However, mothers of infants who are enrolled but subsequently not randomized will be terminated and have no further study follow-up or evaluations.

### Version 2.0 Maternal Follow-Up

Mothers of infants randomized under Version 2.0 of the protocol that consented for continued participation will remain in the study and be followed 18 months according to the schedule described above.

Mothers of infants enrolled under Version 2.0 of the protocol and were not randomized (including those enrolled on or after 10 August 2007) that consented for continued participation will be followed according to the study schedule described above through the Month 3 visit only and will then be terminated from the study.

See Section 9.3 for a description of the HIV-related care that will be provided to mothers.

## **2.2 Version 3.0 Infant Enrollment, Randomization, and Follow-Up**

Infants will be enrolled in the study within 7 days after birth. All infants in the study will receive open-label NVP for the first 6 weeks (42 days) of life. Depending on the day of enrollment, mothers will be instructed to begin administration of open-label NVP after enrollment on any day from Day 3 through Day 7 and continue daily administration of open-label NVP through 6 weeks (42 days) of age.

Randomization of eligible infants will be targeted for the 6 week visit (Day 42); infants may be randomized up until 8 weeks (56 days) of age. See section 4.3 for randomization criteria. Infants will be randomized to one of two arms, either NVP or NVP placebo and begin study drug dosing at  $\geq 43$  days of age. See section 6.2 for treatment dose and administration procedures. Infants will continue study drug from age 6 weeks through 6 months or through cessation of breastfeeding, whichever is earliest.

Adherence to the infant dosing regimen will be assessed at each maternal/infant visit by interview. (In addition, adherence will be assessed by measurement of NVP concentration levels in stored plasma samples from infants who become infected and from a sample of uninfected infants.)

Described below are the required clinical and laboratory procedures for infants; see also Section 5 and Appendix I B for a schedule of infant evaluations. Physical examinations and medical histories, as outlined in the SSP manual, will be conducted on infants at enrollment, 2, 5, 6, and 8 weeks and 3, 4, 5, 6, 9, 12, and 18 months. Blood samples for the following assays will be drawn at birth (on or before Day 7 after delivery), 2, 5, 6 and 8 weeks and 3, 6 and 12 months: ALT (up to 6 months) and CBC with differential (excluding 8 weeks). CD4+ cell counts will be done on infants with confirmed HIV infection at 2 and 6 weeks and 3, 6, 12 and 18 months. Plasma will be stored at birth (on or before Day 7 after delivery), 2, 5, 6 and 8 weeks and 3, 6, 12 and 18 months for retrospective evaluations of NVP resistance, HIV-1 RNA PCR copy number and NVP concentrations in infants determined to be HIV-infected. Dried blood spots will be stored at birth (on or before Day 7 after delivery), 2, 5, 6 and 8 weeks, 3, 6, 9, 12, and 18 months for back-up

testing. A sample of HIV uninfected infants will also be retrospectively tested for NVP concentrations.

The HIV-1 DNA PCR assay will be run at the sites in real time at birth (on or before Day 7 after delivery), 2 and 5 weeks and 3,6,9, and 12 months. At 18 months, an HIV EIA or rapid HIV test will be performed. Cell pellets will be stored at birth (on or before Day 7 after delivery), 2, 5, 6 and 8 weeks and 3, 6, 9 and 12 for later quality assurance and HIV-1 DNA PCR testing. Any infant with a positive virologic assay (either positive HIV-1 DNA PCR or Western Blot or IFA at 18 months) will have a repeat assay drawn on a different day to confirm infection status. Infants confirmed as HIV-infected will be permanently taken off of drug (either NVP if  $\leq 6$  weeks (42 days) of age or study drug if  $>6$  weeks of age) but will remain in follow-up and undergo all study assessments except adherence assessment and HIV testing through 18 months if randomized and through 3 months if not randomized. See section 9.3 for a description of the clinical care that will be provided to HIV-infected infants. Evaluation of clinical, immunologic and virologic disease progression in infected infants will be based on physical examination, medical history, CD4+ cell counts and HIV-1 RNA PCR. CBC with differential will be drawn on HIV-infected infants at 18 months of age.

All infants who are enrolled but subsequently not randomized will continue scheduled study follow-up and evaluations, primarily for safety evaluation, through the 3 month visit and then be terminated.

Note: Infant blood amounts are expected to be limited; therefore priorities for laboratory assays will be specified in the SSP Manual.

Note: Quantitative HIV-1 RNA PCR may be used as an alternative for infant diagnosis if HIV-1 DNA PCR is not available.

### **2.3 Version 2.0 Infant Follow-Up**

All infants randomized under Version 2.0 of the protocol whose mothers consent for continued participation will remain in the study and be followed 18 months according to the schedule described above.

Infants enrolled under Version 2.0 of the protocol who were not randomized (including those enrolled on or after 10 August 2007) and whose mothers consent for continued participation will be followed according to the study schedule described above through the Month 3 visit only and will then be terminated from the study.

### **2.4 Diagnostic Testing to Determine HIV Infection**

The DNA test that is currently available for diagnosis of infant HIV infection is currently is a non-FDA-approved “research use only” assay by Roche Diagnostic Systems. It uses the same primers that are now incorporated into the Amplicor HIV-1 Monitor assay version 1.5, which is the most current version of the RNA PCR assay that is in use to quantitate plasma RNA copy number. The currently available version 1.5 Amplicor DNA and FDA-licensed RNA PCR assays, which are highly sensitive for detection of subtype B HIV and have been shown in several studies to have increased sensitivity to non-subtype B strains, including those subtypes A, C and D that commonly occur in the HPTN 046 study sites (83,85,86). In a study of the Roche Amplicor version 1.0 and 1.5 DNA PCR assays in 106 HIV-infected and 55 seronegative

Tanzanian pregnant women with HIV subtype A, C and D infection, the Amplicor version 1.5 had higher sensitivity for detection of HIV-1 DNA than the standard version 1.0 assay (99.1% versus 97%, respectively) (84).

Some studies have suggested that HIV-1 RNA assays may be more sensitive for diagnosis of infant HIV infection than DNA PCR (87,88). However, the studies have not evaluated the sensitivity of such tests in the presence of maternal antiretroviral therapy (in some sites, antiretroviral therapy may become available for treatment during the course of the study) or in the case of continued antiretroviral prophylaxis as will be studied in HPTN 046. It is known in antiretroviral treated individuals that although free virus as detected by HIV-1 RNA can become undetectable, cell-associated HIV as detected by HIV-1 DNA remains positive. Therefore, the HIV-1 Amplicor DNA 1.5 PCR assay is the preferred test for diagnosis of HIV infection in infants in this study. However, if the DNA PCR assay is not available at the study sites for any reason, quantitative HIV-1 RNA PCR will be used as an alternative for infant diagnosis, as the Roche RNA assay would be appropriate for use to detect non-subtype B infection.

### **3.0 STUDY OBJECTIVES**

#### **3.1 Primary Objectives**

The primary objectives of this study are to:

1. Compare the rate of HIV infection at 6 months in infants determined to be HIV uninfected at 6 weeks in each arm.
2. Evaluate and compare the safety and tolerance in infants in each arm.

#### **3.2 Secondary Objectives**

The secondary objectives of this study are to:

1. Compare the proportion of infants who are alive and free of HIV at 6 months and 18 months of age in the two arms.
2. Compare the relative rates of HIV infection in infants over 18 months in the two arms.
3. Compare the infant survival rates (mortality regardless of HIV infection) over 18 months in the two arms.
4. Determine the frequency and duration of NVP-resistant HIV strains in maternal plasma and breast milk and the relationship with MTCT.
5. Determine the relationship of maternal plasma and breast milk RNA levels to risk of MTCT.
6. Determine the frequency, type, and duration of NVP-resistant HIV strains in the plasma of infants who become HIV-infected.
7. Compare the rates of HIV disease progression, as defined by CD4+ cell count, HIV-1 RNA copy number, and mortality between the two arms in infants who become HIV-infected.

8. Determine NVP concentrations in infants who become infected with HIV and a sample of HIV uninfected infants as an index of adherence to the NVP regimen.

#### **4.0 STUDY POPULATION**

This study targets enrollment of 1670 HIV-infected women and their breastfeeding infants to achieve the target of 1500 infants randomized at 6 weeks. In addition approximately 250 mother/infant pairs originally enrolled under Version 2.0 will be followed under Version 3.0. HIV-infected pregnant women will be recruited from antenatal clinics at DAIDS Clinical Trials Sites in Zimbabwe, South Africa, Uganda, Tanzania and/or other locations.

##### **4.1 Maternal Eligibility Criteria**

Women must meet all of the following criteria to be eligible for the study:

- $\geq 18$  years of age
- Willing and able to provide study informed consent
- Third trimester of pregnancy or on or before Day 7 after delivery
- HIV-infected, as evidenced by 2 positive EIA's; or 1 positive EIA or rapid test and 1 positive WB; or 2 separate positive rapid tests (WHO acceptable diagnostic HIV-1 infection criteria for adults)
- No serious medical condition that would interfere with participation in the study (e.g. a condition that would prevent breastfeeding or adherence to the follow-up schedule), as judged by the on-site clinician.
- Intend to breastfeed
- If not already delivered: Intend to deliver at a facility where the study is based

Note: Women who are receiving or have received antiretrovirals (including NVP) for treatment of HIV or for prevention of MTCT *are* eligible. Mothers will be considered enrolled in the study at the point of infant enrollment (within 7 days after birth).

##### **4.2 Infant Enrollment Criteria**

Infants must be enrolled on or before Day 7 post delivery. See Section 6.2 for dosing and administration procedures for open-label NVP. Infants must meet the following criteria for enrollment:

- Born to an HIV-infected mother who is eligible and has consented to take part in this study
- HIV-1 DNA PCR negative from a specimen obtained on or before 7 days of life (Quantitative HIV-1 RNA PCR may be used if HIV-1 DNA PCR is not available.)
- Birthweight of at least 2000 gm
- Able to breastfeed (i.e., mother and infant alive with no condition apparent that would preclude breastfeeding)

Infants who meet any of the following criteria will be excluded from enrollment into the study:

- ALT from birth specimen is Grade 2 or higher.

- Hemoglobin, absolute neutrophil count or platelet count from birth specimen is Grade 3 or higher
- Skin rash grade 2B (urticaria) or skin rash grade 3 or above
- 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.
- Serious illness or condition that would prohibit compliance with study procedures as judged by site clinician

In the case of a multiple birth, infants will be included in the study only if both/all are eligible for enrollment. If only one infant of a multiple birth is alive, the infant may be enrolled if he/she otherwise meets all of the criteria.

### 4.3 Infant Randomization Criteria

The target randomization day for infants will be at the 6 week post-delivery visit; however, infants who meet the randomization and study drug initiation criteria may be randomized at any time from 6 weeks (42 days) through 8 weeks (56 days) of life and begin study drug dosing at  $\geq$  43 days of life. See Section 6.2.3 for initial dosing procedures following randomization. Infants who initiated the 6-week NVP regimen will be eligible for randomization regardless of whether they completed the regimen provided that they meet the criteria below.

Infants must meet the following criteria for randomization:

- HIV-1 DNA PCR negative from a specimen obtained at the week 5 visit (Note: A negative result on a specimen obtained later (e.g., at the 6 week visit) is acceptable, provided that the result is available prior to randomization on or before 8 weeks (Day 56). No more than 21 days are allowed between collection of the specimen for testing (with negative result) and randomization on or before 8 weeks (Day 56)).
- Still breastfeeding and intending to continue breastfeeding

Infants who meet any of the following criteria will be excluded from randomization:

- The infant required permanent discontinuation of open-label NVP given during the first 42 days of life
- An infant never initiated the open-label NVP regimen
- Current grade 3 hematologic abnormalities that are deemed related or probably related to open-label NVP or any current grade 4 hematologic abnormality
- Current grade 2 or higher ALT
- Current skin rash grade 2B (urticaria)
- Current grade 3 or 4 skin rash
- 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.
- Serious illness or condition that would prohibit compliance with study procedures as judged by site clinician
- Required concomitant use of rifampin or oral ketoconazole

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

Note: Results of the week 6 study visit laboratory tests are not required prior to randomization or dispensing of study drug, but conditions listed above are exclusionary if known prior to randomization/dosing.

In the case of a multiple birth, infants will be randomized only if both/all are eligible for randomization and will be randomized to the same study arm.

## **5.0 STUDY PROCEDURES**

An overview of the study visit and procedures schedule is presented in Sections 2.0-2.2 and Appendices IA and IB. Presented below is additional information on visit-specific study procedures.

### **5.1 Screening and Follow-up Maternal Evaluations**

#### **5.1.1 Maternal Eligibility Evaluations: third trimester of pregnancy/on or before Day 7 postpartum**

##### ***Clinical Evaluations and Instructions***

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

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

##### ***Laboratory Evaluations***

- Confirmatory HIV test (if needed)
- CBC with differential
- CD4+ cell count
- Plasma storage for HIV-1 RNA PCR and NVP resistance testing
- Dried blood spot storage for back-up testing

Note: The specimen storage consent (see Appendix II C) is for storage and testing of samples that are not required by the study protocol. Women who choose to participate in the study do not have to provide consent for specimen storage to be enrolled. Storage of specimens not required by the study protocol is optional for study sites.

5.1.2 Maternal Labor and Delivery Evaluations: as close to delivery as possible but on or before Day 7 after delivery

Note: For women who are screened after labor and delivery, the evaluations for the Screening and Labor/Delivery visits can be *combined into one visit*; duplicate blood work does need not to be done.

***Clinical Evaluations and Instructions***

- Infant feeding options counseling
- Medical history
- Physical exam
- Instructions for administration of infant study drug

***Laboratory Evaluations***

- CBC with differential
- CD4+ cell count
- Plasma storage for HIV-1 RNA PCR and NVP resistance testing
- Dried blood spot storage for back-up testing

5.1.3 Maternal Follow-up Evaluations

Note: If the infant is not randomized for any reason, maternal follow-up will be discontinued immediately and no further evaluations will be done.

***Clinical Evaluations and Instructions (2 and 6 weeks and 3, 6, 12, and 18 months)***

- Interim medical history
- Symptom directed physical exam
- Infant feeding options counseling
- Instructions for administration of infant study drug (2 and 6 weeks and 3 months only or as long as the infant is receiving study drug)
- Confirmation of intent to continue breastfeeding (6 weeks only)

***Laboratory Evaluations (2 and 6 weeks and 3, 6, and 12 months)***

- CBC with differential
- CD4+ cell count
- Plasma storage for HIV-1 RNA PCR and NVP resistance testing
- Breast milk storage (as long as the infant is breastfeeding or through 12 months, whichever is sooner.)
- Dried blood spot storage for back-up testing

***Laboratory Evaluations (18 months)***

- Plasma storage for NVP resistance testing
- Dried blood spot storage for back-up testing

## 5.2 Infant Enrollment and Follow-up Evaluations

### 5.2.1 Infant Evaluations Prior to Enrollment (on or before Day 7 of life)

#### *Clinical Evaluations*

- Birth and neonatal history, including antenatal and or NVP exposure.
- History: general and potential drug reactions
- Physical examination
- Confirmation of mother's intent/ability to breastfeed

#### *Laboratory Evaluations*

- CBC with differential
- ALT
- Real-time Roche Amplicor HIV-1 DNA PCR testing (Note: Quantitative HIV-1 RNA PCR may be used if HIV-1 DNA PCR is not available.)
- Cell pellet will be stored for quality assurance testing.
- Plasma storage for NVP resistance, HIV-1 RNA PCR, and NVP concentrations
- Dried blood spot storage for back-up testing

### 5.2.2 Follow-up Infant Evaluations

Note: Evaluations through Month 3 will be performed on all infants enrolled under Version 2.0 or 3.0 of the protocol; evaluations thereafter will be performed only on infants who were randomized under either Version 2.0 or Version 3.0 of the protocol.

#### *Clinical Evaluations (2, 5, 6, and 8 weeks, and 3, 4, 5, 6, 9, 12, and 18 months)*

- History (general and potential drug reaction)
- Infant feeding practices assessment
- Physical examination
- Adherence assessment (maternal interview) (at 2, 5, 6 and 8 weeks, 3, 4, 5, and 6 months only)
- Confirmation of mother's intent to continue breastfeeding (6 weeks only)

#### *Laboratory Evaluations (at 2, 5, 6 and 8 weeks and 3, 6, 9, 12, and 18 months)*

- CBC with differential (at 2, 5 and 6 weeks and 3, 6, and 12 months in all infants and at 18 months in infants determined to be HIV-infected)
- ALT (at 2, 5, 6 and 8 weeks and 3 and 6 months)
- Real-time Roche Amplicor HIV-1 DNA PCR testing (at 2, and 5, weeks and 3, 6, 9 and 12 months only.) If positive, repeat test on a second sample on or before the participant's next scheduled visit for confirmation, see section 8.6.1. (Note: Quantitative HIV-1 RNA PCR may be used if HIV-1 DNA PCR is not available.)
- Cell pellets will be stored for back-up HIV-1 DNA PCR (at 6 and 8 weeks) and quality assurance testing (at 2, 5, 6 and 8 weeks and 3, 6, 9 and 12 months).



- Plasma storage for NVP resistance, HIV-1 RNA PCR and NVP concentrations (at 2, 5, 6 and 8 weeks and 3, 6, 12, and 18 month), See section 8.6.1
- HIV EIA or rapid HIV test (at 18 months only). If positive, confirm with a Western Blot or IFA on the first sample and confirm with a Western Blot or IFA on a second sample drawn on a different day.
- CD4+ cell count (for infants with confirmed HIV infection only at 2 and 6 weeks and 3, 6 12, and 18 months)
- Dried blood spot storage for back-up testing (at 2, 5, 6 and 8 weeks and 3, 6, 9, 12, and 18 month)

Note: If an infant has a single test suggesting HIV infection, the mother is to be contacted and asked to bring the infant to the clinic for a confirmatory test as soon as possible and no later than the next scheduled study visit. Should an infant be confirmed as HIV-infected at any time during the study, that infant will permanently be taken off of open-label NVP if  $\leq 6$  weeks of age or study drug if  $> 6$  weeks of age.

If open-label NVP is permanently discontinued prior to randomization for any reason (e.g., HIV infection, cessation of breastfeeding, toxicity) the infant will not be randomized and will remain in follow-up through the 3 month visit only and then be terminated from the study; his/her mother will have no further assessments done and will be terminated immediately.

If study drug is permanently discontinued after randomization for any reason (e.g., HIV infection, cessation of breastfeeding, toxicity), the randomized infant and his/her mother will remain in follow-up for 18 months and undergo all scheduled evaluations as described in Section 5.4, with the exception of adherence assessment.

### **5.3 Maternal Evaluations in the Case of Early Withdrawal**

All mothers of randomized infants completing the 18-month evaluation visit will have fulfilled the maternal clinical and laboratory evaluation requirements for the study. Enrolled mothers of randomized infants who discontinue the study prior to the 18-month evaluation will have the following clinical and laboratory evaluations performed, if possible, but will also be discontinued from the study:

- Interim medical history
- Symptom directed physical exam
- Plasma storage for HIV-1 RNA PCR and NVP resistance
- Dried blood spot storage for back-up testing

### **5.4 Infant Evaluations in the Case of Treatment Discontinuation or Study Withdrawal**

All randomized infants completing the 18-month evaluation schedule will have fulfilled the infant clinical and laboratory evaluation requirements for the study.

#### Randomized infants off study drug/on study

All randomized infants who are prematurely discontinued from study drug will be considered *off study drug/on study* and will follow the same schedule of events as those infants who continue

study treatment except adherence assessment. All of these infants will be followed through 18 months as scheduled.

Randomized infants prematurely discontinued from the study before the 6-month evaluation will have the following clinical and laboratory evaluations performed, if possible:

- History
- Physical exam
- Infant feeding practices assessment
- CBC with differential and platelet count
- ALT
- Roche Amplicor HIV-1 DNA PCR and cell pellet storage
- Plasma for storage (for NVP resistance, HIV-1 RNA PCR and NVP concentration)
- Dried blood spot storage for back-up testing

Randomized infants prematurely discontinued from the study at any time after the 6-month evaluation will have the following clinical and laboratory evaluations performed, if possible:

- History
- Physical exam
- Roche Amplicor HIV-1 DNA PCR and cell pellet storage
- Plasma for storage (for NVP resistance, HIV-1 RNA PCR and NVP concentration)
- Dried blood spot storage for back-up testing

Note: Quantitative HIV-1 RNA PCR may be used if HIV-1 DNA PCR is not available.

## **5.5 Participant Retention**

Once an infant is enrolled or randomized, the study site will make every reasonable effort to follow the infant for the entire study period (through Month 3 if not randomized, through Month 18 if randomized). It is projected that the rate of loss-to-follow-up on an annual basis will be at most 5% (see Section 8.3.1). Study site staff are responsible for developing and implementing local standard operating procedures to achieve this level of follow-up.

## **5.6 Participant Withdrawal**

Participants may withdraw from the study for any reason at any time. The investigator also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the Protocol Chair, National Institutes of Health (NIH) Medical Officers, Statistical and Data Management Center (SDMC) Protocol Statistician, and Coordinating and Operations Center (CORE) Protocol Specialist.

Participants also may be withdrawn if the study sponsor or government or regulatory authorities terminate the study prior to its planned end date.

Note: Early discontinuation of study product for any reason is not a reason for withdrawal from the study.

## **5.7 Toxicity Management in the Infant**

Management of any adverse event will be according to the best clinical practice available and the judgment of the site investigator or designated clinician. If adverse events occur, open-label NVP or study drug may be temporarily held or permanently discontinued. Clinical decision making for temporarily holding or permanently discontinuing open-label NVP or study drug will be based on clinical judgment and on the severity grade of the AE observed as outlined in the Toxicity Management Table in Appendix IV.

The first 12-16 weeks of therapy with NVP is a critical period during which intensive monitoring of patients is necessary to detect potentially life-threatening hepatic events and skin reactions.

All randomized infants and their mothers will complete the 18 months of follow-up as scheduled, regardless of whether the study drug regimen was discontinued early.

## **5.8 Infant Concomitant Medications**

Infant systemic medications including only antibiotics, antiretrovirals, antifungals, and antimicrobicides used in infants will be recorded on applicable study case report forms through 8 months of life. Mothers' reported receipt of other antiretrovirals will also be assessed at each infant follow-up visit while breastfeeding to record infant exposure via breast milk.

## **5.9 Infant Co-Enrollment**

Participants will be discouraged from participating in other clinical trials of investigational agents however participants will not be prevented from joining a study which would provide access to HIV-related or other treatment to which they would otherwise not have access.

# **6.0 STUDY TREATMENT/PRODUCT/INTERVENTION**

## **6.1 Treatment Formulation and Content**

Open-label NVP for the initial 6 week regimen, and study drug, NVP (supplied as 10 mg/ml oral suspension) and NVP placebo, will be provided by Boehringer Ingelheim Pharmaceuticals Inc. and is to be stored at the study site at 15°C - 30°C. Daily temperature monitoring is required to document storage conditions.

## **6.2 Treatment Dose and Administration**

Infants who meet randomization criteria under Version 3.0 of the protocol (see Section 4.3) will be randomized to one of two treatment arms described in the table below. All enrolled infants will receive open-label NVP prophylaxis for the first 6 weeks (42 days) of life as part of HPTN 046, and those eligible will initiate the randomized blinded study drug regimen at age 6 weeks (43 days) and continue dosing through first 6 months of life or until cessation of breastfeeding, whichever is earliest. Cessation of breastfeeding is defined as completely ceasing all exposure to breast milk for at least 30 days.

Mothers will receive syringes and instructions and at least enough study product (either open-label NVP or study drug) to dose their infant until the next scheduled visit. Clinic staff may request additional study product (either open-label NVP or study drug) and syringes in the event that the mother cannot return to the clinic on the infant's scheduled visit date but can return

within the infant's visit window. If a mother informs the site staff that the infant will not be able to return for a follow-up visit during the entire next visit window, the mother will not receive any further study product (either open-label NVP or study drug) until the infant is able to return to the clinic. Site staff may not authorize dispensation of any additional supply of study product (either open-label NVP or study drug) or oral syringes that would be used in the event of a missed visit window because infants need to be seen to be properly evaluated for possible toxicities. Details of this distribution can be found in the SSP manual.

The open-label NVP and study drug regimen will be based on infant age and administered using an oral syringe with calibrations to 0.2 ml. Any infant who vomits within 60 minutes of study product (open-label NVP or study drug) dosing may be redosed one time following the first dose. Infants determined to be HIV-infected will be taken off of study product (open-label NVP or study drug) but will remain in study follow-up (for 3 months if determined to be HIV-infected prior to randomization, or the full 18 months if determined to be infected following randomization).

**Infant Treatment Regimen:** Infants eligible under Version 3.0 of the protocol will be enrolled in the study on or before Day 7 after birth. All infants enrolled under 3.0 of the protocol will receive a daily regimen of open-label NVP through 6 weeks (42 days) of life starting after enrollment at 3 to 7 days of life. Infants still eligible at 6 weeks of age will be randomized to one of two study arms and will initiate the daily study drug regimen (NVP or NVP placebo), as outlined below. Infants enrolled under Version 2.0 of the protocol who were either randomized to the placebo arm and over 6 weeks ( $\geq 43$  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 according to the age-appropriate dose specified below. Infants enrolled under Version 2.0 of the protocol who were not randomized (including those enrolled on or after 10 August 2007) or who were randomized to the placebo arm of the study and under 6 weeks ( $< 43$  days) of age as of 10 August 2007 will be provided open-label NVP with dosing as specified below through six weeks (42 days) of age. Infants determined to be HIV-infected will be taken off of open-label NVP (if  $< 6$  weeks of age) or study drug but will remain in follow-up as scheduled.

<b>Infant Dosing Regimen</b>	
<b>All enrolled infants less than 43 days of age will receive:</b>	
<b>NVP suspension (10 mg/ml) N<math>\approx</math>1670</b>	0.6 ml (6 mg) once daily from 3 to 7 days after birth to 2 weeks of age 1.5 ml (15 mg) once daily from 2 to 5 weeks of age 1.8 ml (18 mg) once daily from 5 to 6 weeks (42 days) of age
<b>Eligible infants (N=1500) will be randomized at approximately 6 weeks to receive either:</b>	
<b>NVP Suspension (10 mg/ml) (n=750)</b>	2 ml (20 mg) once daily from 6 ( $\geq 43$ days of age) to 8 weeks of age 2.2 ml (22 mg) once daily from 8 weeks to 3 months of age 2.4 ml (24 mg) once daily from 3 to 4 months of age 2.6 ml (26 mg) once daily from 4 to 5 months of age 2.8 ml (28 mg) once daily from 5 to 6 months of age
<b>NVP Placebo (n=750)</b>	2 ml once daily from 6 to 8 weeks of age 2.2 ml once daily from 8 weeks to 3 months of age 2.4 ml once daily from 3 to 4 months of age 2.6 ml once daily from 4 to 5 months of age 2.8 ml once daily from 5 to 6 months of age

*Note:* Local standard of care antiretroviral regimen for prevention of *in utero*/intrapartum mother to infant HIV transmission will be offered to all mothers and infants (outside of the study) regardless of their participation in HPTN 046.

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

dose adjustment at only two days prior to the target age of two weeks. Randomized infants will begin the six week dose adjustment at  $\geq 43$  days of age.

*Note:* Infants enrolled under Version 2.0 will follow the dosing schedule in protocol Version 2.0, which requires a dose adjustment at 4 weeks of age rather than at 5 weeks of age, until the site has all approvals and is registered under Version 3.0, at which time, the dosing schedule above will be followed.

#### 6.2.1 Initial Open-Label NVP Dosing Criteria (through First 6 Weeks (42 days) of Life)

Mothers and their infants have to be enrolled on or before Day 7 after birth. Mothers will be instructed to begin dosing of NVP to the infant on any day from Day 3 through Day 7, with the day of birth considered Day 0. If at a subsequent study visit, study staff learn that administration of NVP was not administered and the infant continues to meet the dosing criteria specified below and has been exposed to breast milk within the last 30 days the mother will be instructed to begin NVP dosing as soon as possible at the appropriate dose for the infant's age.

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 Manual and at the following website: <http://rcc.tech-res-intl.com>)

Infants must meet the following criterion for initial dosing:

- ◆ Negative HIV DNA PCR from a specimen drawn at the current visit or within the previous three weeks ( $\leq 21$  days). (Note: Quantitative HIV-1 RNA PCR may be used if HIV-1 DNA PCR is not available.)

If any of the conditions bulleted below are known prior to dosing in an infant who has been enrolled, the first dose of open-label NVP should be withheld and the following procedures should be followed.

- ◆ Abnormal lab results as specified below. Test should be repeated within 72 hours or as soon as possible. If the repeat lab test result does not show resolution to Grade 1 for ALT or Grade 2 for blood count parameters, as judged by the on-site clinician, the tests can be repeated. If repeated results do not show resolution of the abnormalities within 7 days, then dosing should not be started.
  - Current ALT of Grade 2 or higher.
  - Current hemoglobin, absolute neutrophil count or platelet count of Grade 3 or higher.
- ◆ Suspected clinical hepatitis, defined as clinical signs and symptoms of clinical hepatic dysfunction, regardless of ALT values, including enlarged liver ( $>4$  cm below right costal margin), hepatic tenderness, ascites.

If clinical hepatitis is confirmed, NVP dosing should not be started.

- ◆ Grade 2B rash (urticaria): NVP should not be started. If rash resolves within 7 days NVP can be started. If rash remains at Grade 2B or higher for more than 7 days, NVP should not be started.
- ◆ Grade 3 or 4 skin rash: NVP should not be started.

The occurrence of these baseline abnormalities is expected to be very rare based on data from HIVNET 012, the PETRA Study, and HIVNET 023.

Note: Infants who do not initiate the open-label regimen of NVP will not be eligible for randomization at 6 weeks.

#### 6.2.2 Conditions for Exclusion from Subsequent Doses of Open-Label NVP (through 6 weeks (42 days) of life)

If an infant has initiated open-label NVP, the NVP may be temporarily held or permanently discontinued if:

- Dosing is contraindicated according to the Toxicity Management Table in the Appendix IV
- Dosing is contraindicated for any reason, as judged by the on-site clinician
- Required concomitant use of rifampin or oral ketoconazole
- Infant is determined to be HIV-infected
- Infant ceases to breastfeed (all exposure to breast milk is stopped)

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

Note: Concerns or questions about resumption of open-label NVP dosing in unusual cases should be directed to the PSRT, which will determine how the situation is to be handled.

Note: If open-label NVP is permanently discontinued prior to randomization for any reason (e.g., HIV infection, cessation of breastfeeding, toxicity) the infant will not be randomized and will remain in follow-up through the 3 month visit only and then be terminated from the study; his/her mother will have no further assessments done and will be terminated immediately.

Note: Infants determined to be HIV-infected will have open-label NVP permanently discontinued the infant will not be randomized and will remain in follow-up through the 3 month visit only and then be terminated from the study; his/her mother will have no further assessments done and will be terminated immediately.

#### 6.2.3 Initial and Subsequent Study Drug Dosing Following Randomization

Ideally, infants who meet the eligibility criteria in Section 4.3 will be randomized to study drug at the 6 week visit (with the target being Day 42) and the mother instructed to begin study drug dosing (NVP or NVP placebo) on Day 43 of life. If the infant is randomized after Day 42 (must be on or before 8 weeks (Day 56)), then the mother will be instructed to begin study drug dosing on the day of randomization. See Section 4.3 for randomization procedures. If at a subsequent study visit, the study staff learn that administration of the study drug was not begun within this timeframe the procedures below will be followed.

In a randomized infant, study drug dosing (initial or subsequent) may be temporarily held or permanently discontinued if:

- Dosing is contraindicated according to the Toxicity Management Table in the Appendix IV
- Dosing is contraindicated for any reason, as judged by the on-site clinician
- Required concomitant use of rifampin or oral ketoconazole
- Infant is determined to be HIV-infected
- Infant ceases to breastfeed (all exposure to breast milk is stopped)

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

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

Note: Randomized Infants determined to be HIV-infected will have study drug permanently discontinued but will remain in follow-up as described in Section 5.4.

If study drug is not initiated or permanently discontinued after randomization for any reason (e.g., HIV infection, cessation of breastfeeding, toxicity), the randomized infant and his/her mother will remain in follow-up for 18 months and undergo all scheduled evaluations as described in Section 5.4, with the exception of adherence assessment.

### **6.3 Treatment Supply and Accountability**

Nevirapine 10 mg/ml suspension will be provided by Boehringer Ingelheim Pharmaceuticals, Inc.

Study drugs and oral syringes will be supplied by the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist is required to maintain records of all study drugs received from the CRPMC and subsequently dispensed to study participants. All unused study drugs are to be held until the study is completed or terminated or until otherwise instructed by the sponsor. Specific instructions will be provided by the sponsor for return or destruction of the study products.

### **6.4 Adherence Assessment**

Adherence to the infant dosing regimen will be assessed at every mother/infant visit by interview. Education about dosing will be reinforced at each visit. Whenever possible, remedies will be sought to facilitate dosing in those cases that non-adherence is suspected, for example with home visits and directly observed therapy by the study staff. Adherence will also be evaluated by measurement of NVP concentrations in stored plasma samples obtained during study visits from those infants who become infected with HIV and in a sample of HIV uninfected infants.

## 7.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

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

A serious adverse event (SAE) is any untoward medical occurrence that at any dose that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (April 1996 International Conference on Harmonisation (ICH), Good Clinical Practice: Consolidated Guidance, (ICH E6). Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above may also be considered to be serious. (October 1994 ICH guidance (E2A), Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

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 Expedited Adverse Event Report Form (EAE Reporting Form) available on the RCC website: <http://rcc.tech-res-intl.com> and sent within three business days of site awareness to the DAIDS 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 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 events on a passive basis, i.e., from publicly available information.

Safety monitoring and adverse event reporting for infants enrolled in the study but not randomized will continue only through the three month follow-up period unless there is a significant AE deemed related to the open-label NVP that remains unresolved at the end of that time. Follow-up of the event will continue until resolution/stabilization or to a point in which the PSRT indicates that no further follow-up is required.



Information on all non-serious and serious AEs in randomized 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 drug that must be considered in determining relationships of AEs in HPTN 046 is the daily open-label nevirapine ((NVP)Viramune) regimen begun in infants after enrollment at 3 to 7 days after birth for 6 weeks (42 days) of life and the daily study drug (nevirapine (Viramune) regimen or placebo regimen) from 6 weeks through 6 months of life. Conditions or illnesses in infants occurring before enrollment will be reported as pre-existing conditions, including congenital anomalies.

The study site Investigators are responsible for continuous close safety monitoring of all study participants, and for alerting the study team if unexpected concerns arise. The HPTN SDMC will prepare routine clinical data reports (blinded to treatment assignment) for review by a Protocol Safety Review Team (PSRT) including the NIAID and National Institute of Child Health and Human Development (NICHD) Medical Officers, the Protocol Chair and the Protocol Statistician. The content, format and frequency of the clinical data reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. The PSRT will convene via conference call routinely (approximately every two weeks during the dosing phase of the study and once a month thereafter) or as needed throughout the study to review the data and discuss any potential safety concerns. In addition, the study will be monitored by the NIAID DSMB, as described in Section 8.7.

Information on all AEs included in the study database will be included in reports to the US FDA and other applicable government and regulatory authorities. Site staff will report information on all AEs and SAEs to their Institutional Review Board (IRB)/Ethics Committee (EC) in accordance with applicable regulations and local IRB/EC requirements.

Any exceptions to the reporting criteria or procedures outlined above must be approved in writing by the sponsor and provided to the US FDA and IRBs/ECs in advance of implementation.

## **7.1 Severity Grading**

Severity of AEs will be graded according to 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 SSP Manual and at the following website address: <http://rcc.tech-res-intl.com>) with the following exception:

Cutaneous/skin rash/dermatitis AEs, malnutrition and axillary measured fever will be graded according to the Supplemental Table for Grading the Severity of Cutaneous/Skin Rash/Dermatitis, Malnutrition and Fever (Appendix III).

Any additional exceptions to the standard DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events must be approved by the sponsor and provided to the US FDA and the IRBs/ECs in advance of implementation. When grading laboratory values, normal limits will be defined according to local institutional values for infants and children. Protocol-specified local laboratory results will be reported on standard DataFax local laboratory results CRFs for entry into the study database, and abnormalities will be graded. Lab abnormalities that are asymptomatic or not attributable to a clinical diagnosis will also be reported separately on a standard DataFax AE CRF if the severity grade is  $\geq 3$ .

## **8.0 STATISTICAL CONSIDERATIONS**

### **8.1 Study Design**

This is a Phase III, multi-site, randomized, double blind, placebo-controlled trial. The main purpose of the trial is to evaluate the efficacy and safety of an extended regimen of NVP from 6 weeks to 6 months or through cessation of breastfeeding, whichever is earliest, for prevention of mother-to-child transmission of HIV through breast milk compared with placebo among infants who are provided nevirapine for the first 6 weeks (through Day 42) of life and are HIV-uninfected at age 6 weeks.

### **8.2 Endpoints**

#### **8.2.1 Primary Endpoints**

1. HIV infection at 6 months in infants determined to be HIV-uninfected at 6 weeks enrolled in each arm of the study, as determined by HIV-1 DNA PCR confirmed by a positive assay on a different specimen. (Note: Quantitative HIV-1 RNA PCR may be used if HIV-1 DNA PCR is not available.)
2. Frequency and severity of adverse reactions among participating infants.

#### **8.2.2 Secondary Endpoints**

1. Proportion of infants who are alive and free of HIV at 6 months and 18 months of age in the two arms.
2. Relative rates of HIV infection 18 months in the two arms.
3. Infant survival rates (mortality regardless of HIV infection) over 18 months in the two arms.
4. Frequency and duration of maternal plasma and breast milk NVP-resistant HIV strains and the relationship with HIV transmission.
5. Relationship between maternal plasma and breast milk RNA levels and the risk of MTCT.
6. Frequency and duration of NVP-resistant HIV strains in the plasma of HIV-infected infants

7. Rates of disease progression as defined by CD4+ cell counts, HIV-1 RNA PCR and mortality in the infected infants in the two arms.
8. NVP concentrations in infants determined to be HIV-infected and sample of HIV-uninfected infants.

### **8.3 Accrual, Follow-up, and Sample Size**

#### **8.3.1 Power Calculations the Primary Efficacy Outcome**

The primary efficacy endpoint in this trial is the rate of HIV-1 infection at 6 months, in infants determined to be HIV-uninfected at 6 weeks. Infants determined to be HIV-infected at 6 weeks will be excluded from the analysis of the primary and secondary endpoints. Unless otherwise noted, all statistical analyses presented hereafter will be applied to the cohort of mother/infant pairs in which the infants have been determined to be HIV-uninfected at 6 weeks and randomized under Version 3.0 of the protocol.

Based on results from the SWEN study, it is anticipated that the overall rate of HIV infection in the control arm of this trial will be approximately 2.6% at 6 weeks post birth and approximately 6.7% at six months of age. Therefore, in the control arm, the rate of HIV transmission through 6 months will be approximately 4.2%. A trial with 1450 mother/infant pairs will provide 90% power to detect a reduction in the rate of HIV infection in infants who are uninfected at 6 weeks from 4.2% to 1.4%, using a Pearson chi-square test statistic having a (one-sided) false positive error rate of 0.025. The SIMBA results suggested that transmission between 4 weeks and 6 months could be as low as 0.8% with infant prophylaxis while the MITRA study had a transmission rate of 1.7% between 6 weeks and 26 weeks. The 1.4% rate with study drug used in our calculations is between the two.

Allowing for a potential 3% loss to follow-up between 6 weeks and 6 months, a cohort of 1500 mother/infant pairs in which the infant is determined to be HIV uninfected at 6 weeks will need to be randomized. The actual number of mother/infant pairs who will need to be enrolled at birth will be higher, to account for infants who die or are not eligible for randomization at 6 weeks (e.g., are HIV infected before 6 weeks or no longer breastfeeding), or are lost to follow-up or become HIV positive between birth and 6 weeks. Specifically, if about 10% of enrolled infants die or are not eligible for randomization at 6 weeks, then approximately 1670 mother/infant pairs will need to be enrolled.

Total duration of the study will be approximately 3 to 3.5 years. It is estimated that the period to randomize the 1500 eligible mother/infant pairs will be approximately 18 to 24 months; follow-up of randomized mothers and infants will be through 18 months postpartum.

#### **8.3.2 Power Calculations for Safety Monitoring**

Based on results from HIVNET 012, prevention of MTCT should result in an improvement in 18-month survival from nearly 60% for infected infants to approximately 92.5% for uninfected infants. Hence a regimen that reduces MTCT by 2.8%, through that

effect, should reduce the death rate by 18 months of age by approximately 9 deaths per 1000 infants.

As a result, the surveillance of safety in these trials should be able to detect a regimen-induced increase in serious non-reversible safety risks that would be of that order of magnitude. A trial of 1500 mother/infant pairs would provide approximately 80% power (using the standard 2.5% false positive error rate) to detect the following increases in rates of such serious AEs in mother/infant pairs:

from 10/1000 to 30/1000, or  
from 1/1000 to 12/1000

Therefore, with safety surveillance that will be conducted in the cohort of mother/infant pairs participating in the HPTN 046 trial, the calculations above indicate that this study will be adequately powered to identify (or rule out) any serious safety risks that would be of the order of magnitude of the clinical benefit that would be attained by the 2.8% reduction in MTCT.

#### **8.4 Random Assignment and Stratification**

A standard principle of trial design is to randomize at a time as proximal as possible to the time that the strategies being assessed differ, thus avoiding losses prior to that time and reducing the sample size. Therefore, infants will be enrolled on or before Day 7 post birth and randomized at age 6 weeks. Randomization will be by site and employ permuted block algorithms with randomized block size. These procedures will be coordinated by the HPTN Statistical and Data Management Center.

To maximize the generalizability of the trial conclusions, maternal use of any antiretrovirals as ongoing therapy is not an exclusion criterion for enrollment. Because it is possible that the use of such therapy during breastfeeding could decrease the rate of MTCT, there will be a balanced randomization across all study sites that is stratified by maternal antiretroviral treatment (none vs any) at the time of randomization (6 week visit).

#### **8.5 Blinding**

Individual study drug kits will be prepared and labeled by the DAIDS CRPMC according to the randomization assignments determined by the HPTN Statistical Center and then sent to the study sites. Randomization and blinding procedures will be coordinated with the Statistical Center and detailed in the SSP manual. Randomized infants will not be unblinded to their randomization assignment unless there is clear justification that such information is required to make decisions about care for that infant.

#### **8.6 Data Analysis**

##### **8.6.1 Primary Analyses**

To account for incomplete follow-up information as well as the stratification at randomization, the primary analysis of the primary endpoint, HIV infection at 6 months, will be based on the difference between intervention groups in Kaplan-Meier estimates of percent free of HIV infection at 6 months, stratified by maternal use of antiretrovirals, and with variances estimated by Greenwood's formula.

The definitions below will be used to determine HIV infection in infants.

*Definition of HIV infection at time of randomization.*

Infants will have blood drawn for HIV testing at the 5 week visit for HIV DNA PCR assay. If negative, the infant will be considered eligible for randomization at the 6 week visit. (Note: A negative result on a specimen obtained later (e.g., at the 6 week visit) is acceptable, provided that the result is available prior to randomization on or before 8 weeks (Day 56)). Infants will have blood stored at the 6 week visit for HIV testing, which will be retrospectively tested in infants found to be HIV-infected at the 3 month visit. If the 6 week HIV DNA PCR is found to be positive in such infants, then the infant will be considered to have been infected *at or prior to 6 weeks* and any data collected will be excluded from the primary and secondary analyses of efficacy and safety.

*Definition of HIV infection.*

An infant less than 15 months of age will be considered to be HIV infected if two separate peripheral blood specimens drawn on different days are each positive by HIV DNA PCR.

Note: Quantitative HIV-1 RNA PCR may be used if HIV-1 DNA PCR is not available.

Infants older than 15 months of age who are reactive for HIV-1 antibody by HIV EIA or rapid HIV test 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.

#### 8.6.2 Analysis of Version 2.0 Cohort

For infants enrolled/randomized under Version 2.0 of the protocol, analyses will include evaluation of drug safety and the relationship of immunologic, virologic, and pharmacologic factors to the risk of perinatal transmission; potentially including but not limited to NVP levels, HIV subtype, and NVP resistance. However, because the controls for infants randomized in Version 2.0 received the single dose (HIVNET 012) intrapartum/neonatal regimen of NVP or another short course ARV regimen for PMTCT and were randomized at birth, while the controls in the revised protocol will receive also receive the 6 week NVP regimen and will be randomized at 6 weeks of age, infants randomized in Version 2.0 are addressing a fundamentally different scientific question than the infants to be randomized under Version 3.0. Therefore, these two data sets cannot be pooled.

### **8.7 Data and Safety Monitoring Procedures**

The duration of the study will be approximately 3.5 years. Accrual will require approximately 18 to 24 months. The primary efficacy assessments will be performed when infants are 6 months of age, and extended efficacy and safety of mothers and infants will be assessed through 18 months postpartum.

The HPTN Study Monitoring Committee (SMC) will monitor study regularly (within 4-6 months of initiation and approximately every six months thereafter) with a focus on issues relating to

quality of trial conduct, such as overall and site-specific rates of recruitment, adherence to study interventions and visit schedules, and retention. A Protocol Safety Review Team including the NIH Medical Officers, the Study Chair and other members of the protocol team will closely monitor clinical study data on a routine basis.

The study will also be monitored by the NIAID DSMB. Administrative and safety data will be reviewed approximately every four to eight months during the first eighteen months of the trial. Primary and secondary endpoint data as well as safety data will be monitored at least annually thereafter.

For interim analyses of efficacy data, the symmetric O'Brien-Fleming group sequential design will be used. It is expected that two formal interim analyses will be conducted at intervals of eight months after the first twelve months of the trial. This symmetric boundary not only provides a guideline for early termination recommendations when interim data are strongly positive, but also guides recommendations for early termination when interim data are sufficiently unfavorable to rule out targeted levels of beneficial effects on the rate of HIV infection.

The NIAID DSMB also could provide a recommendation to terminate or alter the design or conduct of the trial if unacceptable safety results emerge. While the reviews of safety will consider both expected or unexpected adverse events, particular focus will be given to monitoring occurrence of grade 4 hepatitis and serious (e.g., Stevens-Johnson Syndrome) rash, and the relative rates of death. The DSMB will also give careful consideration to emerging evidence about safety and toxicity in relation to infant weight within age strata. The multiplicity of safety measures precludes the development of formal statistical monitoring procedures to guide recommendations about termination. If significant safety concerns emerge, the DSMB will have full access to relevant efficacy and safety data to assess the relative benefit-to-risk profiles of the study regimens when developing their recommendations.

## **9.0 HUMAN SUBJECTS CONSIDERATIONS**

### **9.1 Ethical Review**

This protocol and the template informed consent forms contained in Appendix II will be reviewed and approved by the sponsor and the applicable IRBs/ECs with respect to scientific content and compliance with applicable research and human subjects regulations. All informed consent forms used by the site (local language and English versions) must be approved by the responsible IRBs/ECs prior to consenting any study subjects.

The protocol, site-specific informed consent forms (local language and English versions), participant education and recruitment materials, and other requested documents — and any subsequent modifications — also will be reviewed and approved by the ethical review bodies (IRBs/ECs) responsible for oversight of research conducted at the study site prior to implementation.

Subsequent to initial review and approval, the responsible local Institutional Review Boards/Ethical Committees (IRBs/ECs) will review the protocol at least annually. The Investigator will make safety and progress reports to the IRBs/ECs at least annually and within three months of study termination or completion at his/her site. These reports will include the total number of participants enrolled in the study, the number of participants who completed the

study, all changes in the research activity, all unanticipated problems involving risks to human subjects or others, and summaries of each DSMB review of safety and/or efficacy.

## **9.2 Informed Consent**

Informed consent will be obtained from each study participant (or the parent or legal guardian of participants who cannot consent for themselves) before any study specific procedures are performed. 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. Each study site is responsible for developing a study enrollment informed consent form for local use, based on the templates in Appendix II, which describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The study site also is responsible for translating the template forms into local languages, and verifying the accuracy of the translation by performing an independent back-translation. The specimen storage consent (see Appendix II C) is for storage and testing of samples that are not required by the study protocol. Women who choose to participate in the study do not have to provide consent for specimen storage to be enrolled. Storage of specimens not required by the study protocol is optional for study sites. All informed consent forms used by the site (local language and English versions) must be approved by the responsible IRBs/ECs prior to consenting any study subjects.

Participants (or their parent or legal guardian) will be offered a copy of the informed consent form(s). Study staff will document the informed consent process as described in the study-specific procedures manual. The informed consent form and discussion will outline the risks and benefits of participating in this protocol.

## **9.3 Access to HIV-Related Care**

This study will enroll women who are infected with HIV. At all study sites HIV counseling and testing are provided as part of standard of care (external to the study). All HIV-infected participants – mothers and infants identified during the course of the study - will be referred to available sources of medical and psychosocial care and treatment programs for which they may qualify.

Clinical care provided to HIV-infected mothers and infants may vary by site. At a minimum, mothers and infants will be offered a number of therapeutic benefits including free diagnosis and treatment for their infections, malaria, tuberculosis, and other illnesses. All infants determined to be HIV-infected, are offered bactrim prophylaxis to prevent pneumocystis pneumonia and bacterial infections. All study women or children who require admission to the hospital will receive close monitoring and follow-up. Mothers will be offered nutritional counseling, multivitamins, iron and folate. Each site will develop a plan for the provision of medical care and support to mothers that is consistent with host country standards and policies.

Programs providing HIV care including ART are available and accessible to each of the research sites. Formal links will be established for rapid referral of both infected mothers and infants as appropriate. Study personnel will provide direct and detailed information about HIV-infected infants to the HIV care providers with special emphasis on the NVP prophylactic regimens that the infant received with the potential impact on NVP resistance and its implications for the choice of ART regimen for the infant treatment. In addition, clinical and laboratory evaluations will be

made available to the HIV care providers including results of any available CD4 cell count and viral load testing, which may not otherwise be available in the general ARV treatment settings.

#### **9.4 Incentives**

Pending IRB/EC approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits. Depending on local-IRB requirements site-specific reimbursement amounts may or may not be specified in the study informed consent forms.

#### **9.5 Confidentiality**

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. 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. The use of participant identifiers on study records will comply with the DAIDS SOPs for Source Documentation and Essential Documents.

A participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by the NIAID and/or its contractors; the US FDA, Boehringer Ingelheim; representatives of the HPTN CORE, SDMC, and/or Network Laboratory (NL), the relevant IRBs/ECs, and/or other government and regulatory authorities.

#### **9.6 Study Discontinuation**

The study may be discontinued at any time by the sponsor (US NIAID), the US FDA, Boehringer Ingelheim Pharmaceuticals, the relevant IRBs/ECs or by in-country government or regulatory authorities.

### **10.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT**

#### **10.1 Local Laboratory Specimens**

The following tests will be done at the local laboratory (LL):

- ALT
- CBC with differential
- CD4+ cell count
- Roche Amplicor HIV-1 DNA PCR
- HIV-1 RNA PCR
- Rapid HIV test
- HIV-1 EIA
- HIV-1 Western blot

Note: Only those site labs that meet the ongoing assay certification requirements overseen by the NL will be able to perform the plasma HIV-1 RNA assays locally.



Each study site will adhere to standards of good laboratory practice, the HPTN Manual of Laboratory Operations; and local standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens to the LL. Specimen collection, testing, and storage at the LL will be documented using the HPTN Laboratory Data Management System (LDMS).

The SSP Manual will outline in greater detail the requirements for obtaining and processing these samples.

## **10.2 Network Laboratory Specimens: Storage and Future Testing**

As described in Section 5.0, the following types of specimens will be collected and stored locally. Samples that are identified by the HPTN Network Laboratory (NL) as needed for testing will be requested from the sites and shipped to the NL as follows:

- Plasma (maternal and infant) for determination of NVPR and HIV-1 RNA copy number.
- Dried Blood Spots (maternal and infant) for back-up testing
- Plasma (infant) for determination of NVP concentration.
- Cell Pellet (infant) for HIV-1 DNA PCR and quality assurance testing
- Breast milk for determination of NVPR and HIV-1 RNA copy number

Each study site will adhere to standards of good laboratory practice and the HPTN Manual of Laboratory Operations for proper collection, processing, labeling, and transport of specimens for the NL. All specimens will be shipped in accordance with the International Air Transport Association (IATA) specimen shipping regulations. All shipments will be documented using the HPTN LDMS.

The SSP Manual will outline in greater detail the requirements for obtaining these samples.

## **10.3 Quality Control and Quality Assurance Procedures**

The HPTN NL has established a proficiency-testing program at each study site. NL staff also will conduct periodic visits to each site to assess the implementation of on-site laboratory quality control procedures, including proper maintenance of laboratory testing equipment, use of appropriate reagents, etc. NL staffs will follow-up directly with site staff to resolve any quality control or quality assurance problems identified through proficiency testing and/or on-site assessments.

Throughout the course of the study, plasma/serum samples from all HIV infected infants and an equal number of randomly selected uninfected infants will be retested by the Network Lab. In the event of false positive or false negative HIV result, which changes the endpoint infection status of the subject, a sample from the last visit from all subjects will be retested. In addition, 10% of women enrolled will be retested by the NL for HIV antibody in order to confirm HIV-1 infection. Site laboratory inspections will be done to check for adequate and appropriate collection, handling, storage and shipping of specimens, and general site lab quality assurance.

The NL will inform site staff of the samples selected for quality assurance testing, and site staff will ship the selected specimens to the NL. All specimens will be shipped in accordance with the HPTN NL Manual of Operations (which will be kept at each site) and IATA specimen shipping regulations. All shipments will be documented using the HPTN LDMS.

The NL will test the specimens for HIV antibody and compare the results of their tests with the results obtained by the local labs. NL staff will follow-up directly with site staff to resolve any quality assurance problems identified through this process.

#### **10.4 Biohazard Containment**

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the United States (U.S.) Centers for Disease Control and Prevention (the CDC recommendations are located at <http://www.cdc.gov/od/ohs/biosfty/biosfty.htm>).

### **11.0 ADMINISTRATIVE PROCEDURES**

#### **11.1 Study Activation**

Following ethical review and approval, study sites will submit required administrative documentation — as listed in the SSP manual — to the HPTN CORE. CORE staff will work with study site staff to complete “protocol registration” in accordance with DAIDS procedures. Included in this step will be DAIDS review of each site-specific study informed consent form, including translated and back-translated versions.

Pending successful protocol registration and submission of all other required documents (e.g. local drug authority approval for import of study products), the CORE staff will issue a site-specific “study activation notice” to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site.

#### **11.2 Study Coordination**

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.

The study team and HPTN SDMC will develop study case report forms. Data will be transferred to the HPTN SDMC, entered, and cleaned using the DataFax data management system. Quality control reports and queries will be routinely sent back to the site for verification and resolution.

Close cooperation between the Study Investigators, NIAID and NICHD Medical Officers, Protocol Coordinator, Biostatistician, Data Managers, and other study team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. The study team will monitor rates of accrual, adherence, follow-up, and AE incidence closely. Representatives of the HPTN CORE and SDMC on a regular basis also will evaluate these rates.

### **11.3 Study Monitoring**

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the site to:

- verify compliance with human subjects and other research regulations and guidelines;
- assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and
- confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN CORE, SDMC, NL, NIAID, Boehringer Ingelheim, the International Maternal, Pediatric and Adolescent AIDS Clinical Trials network and US and in-country government and regulatory authorities. A site visit log will be maintained at the study site to document all visits.

### **11.4 Protocol Compliance**

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and the study sponsor (DAIDS). All protocol amendments must be submitted to and approved by the relevant IRB(s)/EC(s) and the DAIDS Protocol Registration Office prior to implementing the amendment.

### **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 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. Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened for and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

### **11.6 Use of Information and Publications**

Publication of the results of this study will be governed by policies of the International Maternal, Pediatric and Adolescent AIDS Clinical Trials network. Any presentation, abstract, or manuscript will be submitted by the Investigator to the HPTN Manuscript Review Committee, DAIDS, and Boehringer Ingelheim for review prior to submission.

## 12.0 REFERENCES

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**APPENDIX I A SCHEDULE OF MATERNAL EVALUATIONS**

Evaluations	Screening	Labor / Delivery (on or before Day 7 pp) <sup>1</sup>	2 wks pp	6 wks pp	3 mos pp	6 mos pp	12 mos pp	18 mos pp
	3rd trimester or on or before Day 7 pp							
Documentation of HIV Status	X							
Confirmatory HIV test (if required)	X							
Study Informed Consent	X							
Demographics	X							
Confirmation of intent to breastfeed	X			X				
Medical history	X	X	X	X	X	X	X	X
Physical examination	X	X	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>
Infant feeding options counseling	X	X	X	X	X	X	X	X
CD4+ cell count	X	X	X	X	X	X	X	
HIV-1 RNA PCR (stored plasma)	X	X	X	X	X	X	X	
NVP resistance (stored plasma)	X	X	X	X	X	X	X	X
CBC with differential	X	X	X	X	X	X	X	
Dried Blood Spot storage	X	X	X	X	X	X	X	X
NVP resistance and HIV-1 RNA (stored breast milk) <sup>2</sup>			X	X	X	X	X	

NOTE: Mothers of infants enrolled under Version 2.0 who were not randomized will complete evaluations through the 3 month visit only. Mothers of infants enrolled under Version 3.0 who were not randomized will complete evaluations until termination at the time the infant is determined to be ineligible for randomization.

wks=weeks, mos=months, pp=postpartum

<sup>1</sup> For women screened prior to labor and delivery only (on or before day 7 postpartum)

<sup>2</sup> Breast milk to be collected and stored as long as infant is breastfeeding from all mothers for future evaluation of NVP resistance and HIV-1 RNA copy number.

<sup>3</sup> Symptom-directed physical exam

**APPENDIX I B SCHEDULE OF INFANT EVALUATIONS**

<b>Evaluations</b>	<b>Enrollment (on or before Day 7 post birth)</b>	<b>2 wks</b>	<b>5 wks</b>	<b>6 wks</b>	<b>8 wks</b>	<b>3 mos</b>	<b>4 mos</b>	<b>5 mos</b>	<b>6 mos</b>	<b>9 mos</b>	<b>12 mos</b>	<b>18 mos</b>
Birth and neonatal medical history	X											
Confirmation of mother’s intent/ability to breastfeed	X			X								
Infant feeding practices assessment		X	X	X	X	X	X	X	X	X	X	X
History (general, potential drug reaction)	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of adherence to infant study regimen		X	X	X	X	X	X	X	X			
CBC with differential	X	X	X	X		X			X		X	X <sup>1</sup>
CD4+ cell count <sup>1</sup>		X		X		X			X		X	X
ALT	X	X	X	X	X	X			X			
Roche Amplicor HIV-1 DNA PCR <sup>2</sup>	X	X	X			X			X	X	X	
HIV EIA or Rapid HIV Test <sup>3</sup>												X
Plasma Storage <sup>4</sup> NVP resistance HIV-1 RNA PCR NVP concentration	X	X	X	X	X	X			X		X	X
Cell Pellet Storage (QA/HIV-1 DNA PCR)	X	X	X	X	X	X			X	X	X	
Dried Blood Spot Storage	X	X	X	X	X	X			X	X	X	X

**wks=weeks mos=months**

Note: Infants enrolled under protocol Version 2.0 or Version 3.0 but not randomized will complete evaluations through the 3 month visit only.

Note: Infants enrolled under protocol Version 2.0 who reached the 4 week time point prior to issuance of Version 3.0 had the 5 week evaluations above done at a scheduled 4 wk visit, not at 5 weeks.

NOTE: Infant blood amounts are expected to be limited; therefore priorities for laboratory assays will be specified in the SSP Manual.

<sup>1</sup> To be done on infants with confirmed HIV infection only

<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. 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 Western Blot or IFA on a second sample drawn on a different day.

<sup>4</sup> Plasma is being obtained and stored on all infants, and will be used to evaluate NVP resistance, HIV-1 RNA copy number and NVP concentrations among those infants found to be HIV-infected. NVP concentration will also be evaluated on a sample of HIV-uninfected infants.

## APPENDIX II A

### SAMPLE STUDY CONSENT FORM FOR INITIAL ENROLLMENT UNDER PROTOCOL VERSION 3.0

**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 3.0, Dated [xx xxx xx]**

**PRINCIPAL INVESTIGATOR:** [Name and Contact Information for the site PI]

#### INTRODUCTION

You are being asked to take part in the research study named above. This is a study for women with HIV who plan to breastfeed their babies. HIV is the virus that causes AIDS. The person in charge of the study at this site is [insert name of PI]. This study is sponsored by the U.S. National Institutes of Health.

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.

Please note that:

- Your participation in this research is entirely voluntary;
- You may decide not to participate or to withdraw from the study at any time without losing the benefits of your and your baby's standard medical care;
- If you decide not to participate in this study, you can still join another research study later, if one is available and you qualify.

#### PURPOSE OF THE STUDY

There are two purposes for this research study. The first is to determine if giving a drug named nevirapine to babies for the first 6 months of life is better at preventing them from getting HIV during breastfeeding than giving nevirapine to the baby only for the first 6 weeks of life. The second is to make sure that nevirapine is safe for babies when given once a day for 6 months.

Mothers who have HIV can pass HIV to their babies before delivery, during delivery, and after delivery through breastfeeding. Other research studies have shown that giving one dose of nevirapine as a pill to mothers at the time of delivery and one dose to babies as a liquid soon after birth can cut the chances of passing HIV to babies during delivery by about half. There are also other drugs that treat HIV infection that can be used to lower the chance of a baby being born with HIV.

Every woman with HIV who comes to this clinic is offered nevirapine or other drugs to help prevent passing HIV to her baby during delivery. You will receive whatever treatment is being given in the clinic for this purpose, whether you choose to join or not to join this research study.

A recent study conducted in Ethiopia, India and Uganda found that giving 6 weeks of the drug nevirapine once a day until the baby was 6 weeks old lowered the chance of passing HIV to the baby through breastfeeding. Because of these results, all babies who join this study will receive nevirapine once a day until the baby is 6 weeks old, even if this is not standard practice yet in this country. The study showed that using nevirapine until age 6 weeks reduces but does not completely prevent the chance of a mother passing the HIV virus to her baby. It is not known if giving nevirapine to babies for a longer time would be even better in cutting the chance of passing HIV to the baby while breastfeeding.

We do not know if nevirapine or any other drug given to the baby every day for more than six weeks is safe or if it will prevent a baby from getting infected with HIV while breastfeeding. This study will help find that out. Currently, the only certain way to prevent passing HIV through breastfeeding is not to breastfeed. As the counselors have discussed with you, there are health risks and benefits to both breastfeeding and not breastfeeding.

This study will include about 2000 mothers and their infants in different countries in Africa and possibly other places. In this country, about [insert site specific number] mothers and infants are expected to join the study.

## **PROCEDURES**

If you agree to join this study and are eligible to join, you may be part of the study from now until your baby is 18 months old. All babies will be given nevirapine liquid to take every day until age 6 weeks to reduce the chance of passing the HIV virus to the baby by breast milk. When your baby is 6 weeks old, the study staff will see if your baby is able to join a second part of the study. If your baby is able to join this second part of the study, he or she will be put into one of two study groups by chance (like tossing a coin). Starting at age 6 weeks, one group of babies will be given nevirapine liquid and the other group will be given a liquid called a placebo. The placebo liquid looks like the nevirapine liquid but does not contain nevirapine or any other medicine. Neither you nor the staff at your clinic will know to which group your baby was assigned until the end of the study. Your baby has an equal chance of being in either group. You and your baby will be asked to stay in the study until your baby is 18 months old. If your baby is not able to join this second part of the study at 6 weeks of age, your baby will keep coming to the clinic until your baby is 3 months old and your participation will end as soon as it is determined that your baby will not be able to join the second part of the study.

### **Mother's Procedures**

Options for feeding your baby have been discussed with you and will be discussed with you throughout the course of the study. The study staff will discuss with you the risks and benefits of both breastfeeding and not breastfeeding. If you decide that you want to breastfeed your baby, you can take part in the study if you otherwise qualify.

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

If you have not already delivered your baby, you will be instructed to come to the clinic as soon as your labor pains begin. You will come to this hospital or clinic to give birth to your baby. You will be asked questions about your health and be asked to give a blood sample (about 10 ml, which is less than one tablespoon) to check your health and to be stored for later HIV-related tests. You will have physical examination soon after delivery (within 7 days). The study staff will tell you if you and your baby are able to join the study.

Study Procedures: If you and your baby are able to join the first part of study, you will be given a bottle of nevirapine liquid and instructions on how and when to give the nevirapine to your baby. All babies will receive the liquid with nevirapine in it. The nevirapine liquid is given to your baby once a day until your baby is 6 weeks old. When your baby is 6 weeks old (or earlier), you will be told if you and your baby are able to join the second part of the study.

If your baby is found to be infected with HIV before age 6 weeks or the study staff find some other reason that your baby should not continue the nevirapine treatment, you will stop giving him or her the nevirapine and your baby will not be able to participate in the second part of the study.

### ***Procedures if you and your baby DO join the second part of the study***

If you and your baby are able to join the second part of the study, you will be asked to come to the study clinic with your baby about eleven times during the 18 months of the study. These study visits will take place at about ages 2, 5, 6, and 8 weeks, then once a month from 3-6 months and then every 3 months through 12 months. A final visit will be when your baby is 18 months old.

You will also have study visits at about 6 of your baby's study visits, with the last visit at 18 months. At these study visits, you will have a physical exam and will be asked about your health. You will also 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 also be asked to give a sample of breast milk (20 ml, which is less than 2 tablespoons) at most visits, to be stored for later HIV-related study tests. 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.

After 6 weeks of age, you will be given a bottle of study liquid that may have nevirapine or placebo in it, depending on the group that your baby was put in by chance, but it will look the same. Neither you nor the staff at your clinic will know whether your baby is swallowing the nevirapine or the placebo. Study staff will tell you how and when to give the study liquid to your baby. It will be given to your baby once a day until your baby is 6 months old or until you stop breastfeeding, whichever is earlier. The study liquid is given to the baby using a syringe that will be given to you by the study staff. You may choose to ask someone in your household to help you remember to give the study liquid to your baby. The clinic and study staff and the home visitors will be aware that you are HIV infected, but they will tell no one. If you choose someone in your household to help you to remember to give the study liquid to your baby, you may or may not decide to tell this person that you are infected with HIV. That is your decision.

### ***Procedures if you and your baby do NOT join the second part of the study***

When the study staff decide that your baby will not be able to join the second part of the study, you will not have any more visits or tests done; however, you will be asked to bring your baby to the clinic for study visits until your baby is 3 months old.

At most, you will have a study visit at 2 weeks and at 6 weeks after delivery. At these visits, you will have a physical exam and will be asked about your health. You will also 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. 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**

#### ***Infant procedures through six weeks of age:***

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 can join the study and a small amount of blood will be drawn (about 5 ml or one teaspoon) to check your baby's health. Some of the blood will also be tested for HIV. If you and your baby are able to join the study, you will be asked to give your baby the nevirapine liquid until the baby is 6 weeks old, as long as you are breastfeeding.

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. Some of the blood taken will be tested for HIV. Your baby will be tested for HIV about 3 times over the first six weeks of the study (including at birth). Some blood will be stored for later HIV-related study tests. 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. 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 infected with HIV, you will be informed as soon as possible. You will stop giving him or her nevirapine liquid.

At 6 weeks, information about your baby's health will be reviewed to see if you and your baby are able to join the second part of the study. Only healthy babies without HIV infection will be able to join the second part of the study. The study staff will let you know if you may join the second part of the study or why you are not able to join.

### ***Infant procedures after six weeks:***

If you and your baby do not join the second part of the study then you will not have any more study visits. However, you will be asked to bring your baby to the clinic for two more visits until your baby is 3 months old. The study staff will check your baby to make sure that he or she does not have any problems from the nevirapine.

If you and your baby do join the second part of the study, you both will continue to come to the study clinic as described earlier for 18 months. You will give your baby the new study liquid that has either nevirapine or placebo in it until your baby is 6 months old or until you stop breastfeeding, whichever comes first.

The scheduled visits for your baby in the second part of the study will be the same as the visits in first part of the study with physical examinations at each visit and blood tests at some visits. Your baby will be tested for HIV about 5 times between 6 weeks and 18 months of age, which is when the study is completed. 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 infected with HIV, you will be informed as soon as possible. You will stop giving him or her study liquid. If you choose to completely stop breastfeeding your baby before your baby is 6 months old, you will also stop giving your baby the study liquid.

### **Weaning**

You will be encouraged by the study staff to stop breastfeeding at the end of 6 months if it is acceptable, feasible, affordable, sustainable and safe for you to do so. Your baby's last dose of study liquid will be given at 6-months or soon after you stop breastfeeding, whichever comes first. If you choose to continue breastfeeding after 6 months you will be given additional counseling on the risk of giving HIV to your baby by continued breastfeeding, but your baby will not get any more study liquid.

### **RISKS and/or DISCOMFORTS**

A number of serious side effects have been associated with nevirapine used in adults and children for treatment of HIV. 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.

Rash is the most common side effect of nevirapine. The rash may be severe and has resulted in hospitalization but rarely in death. One of the risk factors for developing serious skin reactions includes failure to take the nevirapine properly.

Hypersensitivity reactions may occur and may be associated with rash, fever, muscle or joint tenderness, blisters, mouth lesions, facial swelling, red eyes and irritation of the eyes, general irritability, hepatitis, kidney problems and/or changes in white blood cell levels. These conditions have rarely been fatal.

If your infant develops symptoms of any of the serious side effects listed above, you must bring your infant to the study clinic immediately or contact the medical staff at the site. You must do this no matter how long he or she has been receiving either nevirapine until age 6 weeks or study liquid at age 6 weeks or older. The study staff will examine your baby and advise you whether to stop giving the nevirapine or study liquid. If you or the study doctor decides to stop your infant's nevirapine or study liquid because of symptomatic hepatitis, hypersensitivity or severe skin reactions, you should not give your child the nevirapine or study liquid again. Other side effects include fever, headache and upset stomach.



In the studies of babies who received one dose of nevirapine within 2-3 days after birth, or daily nevirapine until 6 weeks of age, no serious rashes or liver problems related to nevirapine were reported. The doses of nevirapine to be given in this study are much lower than those given for treatment of HIV. At these doses, we do not expect babies to experience bad effects from this drug, but we do not know this for sure. In a study of babies who received nevirapine every day, once a week or twice a week for up to 6 months while breast feeding, no serious rash, liver or kidney disease were reported. In that study of infants, nevirapine was found to be safe and well-tolerated. However, the number of babies that have received nevirapine for several months after birth is very small, so we do not know for sure. We will carefully monitor the effects of study liquid on the babies. At the time you and your baby are discharged from the hospital or clinic, you will receive instructions on what to do if you see any rash on you or your baby. It is very important that you come to the study clinic or tell the study doctor or nurse right away about any rash or other problems.

You may feel discomfort when blood is drawn and may feel dizzy or even faint. A bruise may form or swelling may occur where the needle goes in your arm. Your baby will feel discomfort when blood samples are taken. 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.

If your baby has the HIV virus in his or her body at birth, we do not know if giving your baby nevirapine during breastfeeding will make the infection better or worse. Studies in other countries show that adults and children who have the HIV virus and receive only nevirapine do not get any long-term problems or benefits. Nevirapine may prevent HIV infection, but is not good enough to treat HIV infection by itself. If your baby is found to be HIV-infected from blood collected after birth, your baby will not be able to take the daily nevirapine so you and your baby will not be able to join the study. If your baby becomes infected with HIV during this study and is swallowing nevirapine, it may mean that nevirapine and other drugs like nevirapine will not work as well to treat HIV. This is because the HIV virus can adjust to the drug and become resistant to it. This means that drug may not be as useful as part of possible future HIV treatment for your baby. If your baby is found to be infected with HIV, we will make information about the study liquid available to your primary care provider to help with decisions about treatment. If your baby is found to be infected with HIV during the study, you will be advised to stop giving him or her the liquid provided by the study (either the nevirapine liquid given until age 6 weeks or study liquid at age 6 weeks or older). It is likely that your baby will receive some nevirapine or study liquid before it is known that your infant is infected with HIV.

### **POTENTIAL BENEFITS**

You and your baby may receive no benefit from this study. Giving your baby nevirapine for the first 6 weeks of life may decrease the chance of your baby getting the HIV infection from breast milk during that period. However, knowledge gained from this study may in the future help others remain HIV uninfected. You and your baby will receive information about your health from the study examinations and laboratory tests.

Being in this study may reduce the chances of your baby getting HIV, but no guarantee can be made. Although all infants will receive nevirapine liquid for the first 6 weeks of life, after age 6 weeks, your baby may be receiving the study liquid called placebo with no medicine in it. It is also unknown whether the study liquid with nevirapine will prevent your baby from getting HIV while breastfeeding after the infant is 6 weeks old.

### **REIMBURSEMENT**

At each scheduled visit you will receive [insert site-specific amount of money] to pay for your transport costs.

### **NEW FINDINGS**

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study.

### **REASONS WHY YOU OR YOU BABY MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT**

You or your baby may be removed from the study without your consent for the following reasons:

- the study doctor or study staff decides that continuing in the study would be harmful to you or your baby;

- you are unable to keep appointments or take the study product as instructed;
- the study is cancelled by the sponsor (the US National Institutes of Health), the Ministry of Health in this country, [insert other relevant in-country authorities], the US Food and Drug Administration or the pharmaceutical company supplying the nevirapine.
- the Institutional Review Board or Ethics Committee or Data Safety and Monitoring Board (DSMB) recommend that the study be stopped early. (A DSMB is an outside group of experts who monitor the study.)

If you or your baby withdraws from the study early for any reason, you will be asked to undergo a final assessment including a physical examination and blood draw, if possible.

### **ALTERNATIVES TO PARTICIPATION**

You do not have to be in this study if you do not want to. The only known way to prevent passing HIV from a mother to her baby during breastfeeding is not to breastfeed. The clinic and study staff will explain the risk and benefits of breastfeeding to you and about safe alternatives. You will be provided information about where formula may be obtained. If you decide not to participate in the study, you will not lose the benefits of your standard medical care.

The study staff will also refer you to HIV treatment programs that are available in your area. You have a right to consider all options available to you and your baby.

### **COSTS TO YOU**

There is no cost to you for participating in this study. All of study visits and tests and the study drugs for your baby will be provided free of charge.

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.

### **CONFIDENTIALITY**

Your and your baby's research records will be confidential to the extent permitted by law. You will be identified by a code. Personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study. Blood and breast milk collected from mothers, and blood collected from babies as part of this research study will be stored for study tests done later. These specimens will be stored in containers that do not have names on them but rather a code to protect your and your baby's privacy. These samples will be used for tests that are not checking your baby's health. These tests are for learning more about HIV and nevirapine treatment.

Your records may be reviewed by the United States National Institutes of Health (the agency that sponsors this research), the United States Food and Drug Administration, the study monitors, Boehringer Ingelheim (the manufacturer of nevirapine), and [insert name of site IRB].

### **RESEARCH-RELATED INJURY**

Medical care will be provided for illness or injury directly related to this study at no cost to you. Care or appropriate referral will be provided for any illness or injury that occurs during the study that is not directly related to the study, but you may have to pay for this care. There are no plans to give you money if there is a research-related complication or injury.

NOTE: You are not giving up any of your legal rights by signing this informed consent document.

### **PERSONS TO CONTACT FOR PROBLEMS OR QUESTIONS**

If you ever have questions about this study or in case you are injured as a result of participation in this research study, you should contact (Name of local investigator or study clinician) at (telephone number and physical address). If you ever have questions about your rights as a research subject you may call (name and title of IRB member) at (telephone number and physical address).

**STATEMENT OF CONSENT**

I have read the informed consent or had it read and explained to me. I understand the information and I voluntarily agree to join this study.

\_\_\_\_\_  
Mother's name (print)                      Mother's signature or mark                      Date

\_\_\_\_\_  
Father's Name (print)                      Father's Signature or mark                      Date  
(If he is reasonably available)

I observed the informed consent discussion and, to the best of my knowledge, the information provided was complete and accurate. The potential study participant understands the information provided, and she willingly agrees to take part.

\_\_\_\_\_  
Witness' name (print)                      Witness' signature                      Date

I have fully explained the purpose of this study, the procedures, the risk and benefits and other information provided in this consent form to the potential study participant. I have answered all of her questions. To the best of my knowledge, she understands the information provided and willingly agrees to participate in the study.

\_\_\_\_\_  
Investigator's or Designee's                      Investigator's or Designee's Signature                      Date  
Name (print)

## APPENDIX II B

### SAMPLE STUDY CONSENT FORM FOR SUBJECTS ENROLLED UNDER VERSION 2.0 TO CONTINUE IN THE STUDY UNDER VERSION 3.0

**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 3.0, Dated [xx xxx xx]**

**PRINCIPAL INVESTIGATOR:** [Name and Contact Information for the site PI]

#### INTRODUCTION

You are being asked to continue to take part in the research study named above because you agreed to participate previously and were enrolled. This is a study for women with HIV who plan to breastfeed their babies. HIV is the virus that causes AIDS. The person in charge of the study at this site is [insert name of PI]. This study is sponsored by the U.S. National Institutes of Health.

As you may have been informed, some changes have been made to the study that may affect your participation. The changes have been made because of recently learned information from another study conducted in Ethiopia, India and Uganda. That study showed that a drug called nevirapine (the same drug that is used in this study) can reduce the risk of a baby getting infected with HIV through breastfeeding when given to a baby once a day through six weeks of age.

Before you decide whether or not to continue to take part in this research study, you need to know what changes have been made and how they affect 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 changes in the study have been fully explained to you, you can decide whether or not you want to continue participate. Once you understand the study and the changes made and if you agree to continue in the study, 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.

Please note that:

- Your participation in this research is entirely voluntary;
- You may decide not to participate or to withdraw from the study at any time without losing the benefits of your and your baby's standard medical care;
- If you decide not to continue to participate in this study, you can still join another research study later, if one is available and you qualify.

#### PURPOSE OF THE STUDY

There are two purposes for this research study. The first, which has changed since you first agreed to join, is to determine if giving a drug named nevirapine to babies for the first 6 months of life is better at preventing them from getting HIV during breastfeeding than giving nevirapine to the baby only for the first 6 weeks of life. The second is to make sure that nevirapine is safe for babies when given once a day for 6 months.

Mothers who have HIV can pass HIV to their babies before delivery, during delivery, and after delivery through breastfeeding. Other research studies have shown that giving one dose of nevirapine as a pill to mothers at the time of delivery and one dose to babies as a liquid soon after birth can cut the chances of passing HIV to babies during delivery by about half. There are also other drugs that treat HIV infection that can be used to lower the chance of a baby being born with HIV.

Every women with HIV who comes to the clinic is offered nevirapine or other drugs to help prevent passing HIV to her baby during delivery. You will receive whatever treatment is being given in the clinic for this purpose, whether you choose to join or not to join this research study.

Because of the results of the study conducted in Ethiopia, India and Uganda, all babies enrolled in this study will receive nevirapine once a day until the baby is 6 weeks old, although that may not be standard practice yet in this country. It is not known if giving nevirapine to babies for a longer time would be even better in cutting the chances of passing HIV to the baby while breastfeeding.

We do not know if nevirapine or any other drug given to the baby every day for more than six weeks is safe or if it will prevent a baby from getting infected with HIV while breastfeeding. This study will help find that out. Currently, the only certain way to prevent passing HIV through breastfeeding is not to breastfeed. As the counselors have discussed with you, there are health risks and benefits to both breastfeeding and not breastfeeding.

This study will now include about 2000 mothers and babies in different countries in Africa and possibly other places. In this country, about [insert site specific number] mothers and babies are expected to join in the study.

Options for feeding your infant have been discussed with you and will be discussed with you throughout the course of the study. The study staff will discuss with you the risks and benefits of both breastfeeding and not breastfeeding. If you decide that you want to stop breastfeeding your baby, you can remain in the study if you otherwise qualify.

## **PROCEDURES**

The study procedures for you and your baby will depend on your baby's age, when you first joined the study and whether your baby was assigned by chance to one of the study groups.

All babies in the study who are under the six weeks old will now be given nevirapine liquid through 6 weeks of age to reduce the chance of passing the HIV virus to the baby through breastfeeding. The study liquid is given to the baby using a syringe that will be provided to you by the study staff. You may choose to ask someone in your household to help you remember to give the study liquid to your baby. The clinic and study staff and the home visitors will be aware that you are HIV infected, but they will tell no one. If you choose someone in your household to help you to remember to give the study liquid to your baby, you may or may not decide to tell this person that you are infected with HIV. That is your decision.

If your baby was never assigned by chance to any study group, the study staff will have informed you. You and your baby will be asked to stay in the study until your baby is 3 months old. At that point, your participation will be considered complete and you will then be taken off of the study.

If you have not already delivered your baby, you will be instructed to come to the clinic as soon as your labor pains 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 one tablespoon) to check your health and to be stored for later HIV-related tests. You will have physical examination soon after delivery (within 7 days). The study staff will inform you if you and your baby are able to join the study.

If your baby is found to be infected with HIV before age 6 weeks or the study staff find some other reason that your baby should not continue the nevirapine liquid, they will inform you and you will stop giving him or her nevirapine liquid.

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.

### ***Procedures for infants assigned by chance to a study group and their mothers***

If your baby was assigned by chance to one of the two study groups described to you previously, the study staff will inform you. You and your baby will be asked to stay in the study until your baby is 18 months old. After your baby is

born, you will be asked to bring your baby to the study clinic for study visits a total of about 11 times as originally planned when you first joined the study. These study visits will take place at 2, 5, 6 and 8 weeks after your baby is born. After that, the visits will be once a month through 6 months and then every 3 months until 12 months. A final visit will be when your baby is 18 months old.

At each scheduled study visit, your baby will have a physical examination. At most 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. Some of the blood taken will be tested for HIV. Your baby will be tested for HIV about 8 times over the study (including at birth). 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 infected with HIV, you will be informed as soon as possible.

At about six of the baby's study visits (at 2 and 6 weeks and at 3, 6, 12 and 18 months), you will also be asked to 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 also be asked to give a sample of breast milk (about 20 ml, which is less than 2 tablespoons) at most visits, to be stored for later HIV-related study tests. You will have a physical exam and will be asked about your health. Your and your baby's participation will be considered complete at the final 18 month visit and you will then be taken off of the study.

If your baby was over 6 weeks of age as of 10 August 2007, but is currently less than 6 months old, you will continue giving your baby the study liquid to which you were assigned by chance (nevirapine liquid or placebo liquid) for 6 months or until you stop breastfeeding, whichever is earliest. Neither you nor the study staff will know to which group you were assigned until the study is over.

If your baby was under the age of 6 weeks on 10 August 2007 and had been assigned by chance to the group that was to receive the placebo liquid (instead of the nevirapine liquid) the study staff will have informed you. As stated above, your baby will be provided nevirapine liquid through 6 weeks of age.

If your baby is found to be infected with HIV after age six weeks or the study staff find some other reason that your baby should not continue the study liquid, they will inform you and you will stop giving him or her the study liquid. If your baby is permanently stopped from taking nevirapine during the first 6 weeks of life for any reason (even after only one dose), your baby will not be able to receive the study liquid after 6 weeks. You and your baby will continue to be followed for 18 months as planned.

***Procedures for infants never assigned by chance to a study group and their mothers***

If your baby was never assigned by chance to one of the two study groups, the study staff will have informed you. You and your baby will be asked to stay in the study only until your baby is 3 months old. During this time, you will be asked to bring your baby to the clinic a total of about 5 times for study visits. These study visits will take place at Weeks 2, 5, 6, and 8 and Month 3 after delivery.

At each scheduled study visit, your baby will have a physical examination. At each 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. Some of the blood taken will be tested for HIV. Your baby will be tested for HIV about three times during 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 infected with HIV, you will be informed as soon as possible.

At three of the baby's study visits (at 2 and 6 weeks and at three months), you will also 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. You will have a physical exam and will be asked about your health. Your and your baby's participation will be considered complete at the final 3 month visit and you will then be taken off of the study.

## **Weaning**

You will be encouraged by the study staff to stop breastfeeding at the end of 6 months if it is acceptable, feasible, affordable, sustainable and safe for you to do so. If your baby is in the group that is receiving study liquid after 6 weeks, your baby's last dose of study liquid will be given at 6-months or soon after you stop breastfeeding, whichever comes first. If you choose to continue breastfeeding after 6 months you will be given additional counseling on the risk of giving HIV to your baby by continued breastfeeding.

## **RISKS and/or DISCOMFORTS**

A number of serious side effects have been associated with nevirapine used in adults and children for treatment of HIV. These side effects include inflammation of the liver that in rare cases may lead to severe or life-threatening liver damage and death. A baby 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. A baby 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.

Rash is the most common side effect of nevirapine. The rash may be severe and has resulted in hospitalization but rarely in death. One of the risk factors for developing serious skin reactions includes failure to take the nevirapine properly.

Hypersensitivity reactions may occur and may be associated with rash, fever, muscle or joint tenderness, blisters, mouth lesions, facial swelling, red eyes and irritation of the eyes, general irritability, hepatitis, kidney problems and/or changes in white blood cell levels. These conditions have rarely been fatal.

If your infant develops symptoms of any of the serious side effects listed above, you must bring your infant to the study clinic immediately or contact the medical staff at the site. You must do this no matter how long he or she has been receiving either nevirapine until age 6 weeks or study liquid at age 6 weeks or older. The study staff will examine your baby and advise you whether to stop giving the liquid. If you or the study doctor decides to stop your infant's liquid because of symptomatic hepatitis, hypersensitivity or severe skin reactions, you should not give your child the liquid again. Other side effects include fever, headache and upset stomach.

In a study of babies who received one dose of nevirapine within 2-3 days after birth, no serious rashes or liver problems related to nevirapine were reported. The doses of nevirapine to be given in this study are much lower than those given for treatment of HIV. At these doses, we do not expect babies to experience bad effects from this drug, but we do not know this for sure. In a study of babies who received nevirapine every day, once a week or twice a week for up to 6 months while breast feeding, no serious rash, liver or kidney disease were reported. In that study of infants, nevirapine was found to be safe and well-tolerated. However, the number of babies that have received nevirapine for several months after birth is very small, so we do not know for sure. We will carefully monitor the effects of study liquid on the babies. At the time you and your baby are discharged from the hospital or clinic, you will receive instructions on what to do if you see any rash on you or your baby. It is very important that you come to the study clinic or tell the study doctor or nurse right away about any rash or other problems.

You may feel discomfort when blood is drawn and may feel dizzy or even faint. A bruise may form or swelling may occur where the needle goes in your arm. Your baby will feel discomfort when blood samples are taken. 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.

If your baby has the HIV virus in his or her body at birth, we do not know if giving your baby nevirapine during breastfeeding will make the infection better or worse. Studies in other countries show that adults and children who have the HIV virus and receive only nevirapine do not get any long-term problems or benefits. Nevirapine may prevent HIV infection, but is not good enough to treat HIV infection by itself. If your baby becomes infected with HIV during this study and is swallowing nevirapine, it may mean that nevirapine and other drugs like nevirapine will not work as well to treat HIV. This is because the HIV virus can adjust to the drug and become resistant to it. This means that drug may not be as useful as part of possible future HIV treatment for your baby. If your baby is found to be infected with HIV, we will make information about the study liquid available to your primary care provider to help

with decisions about treatment. If your baby is found to be infected with HIV during the study, you will be advised to stop giving him or her the liquid provided by the study (either the nevirapine liquid given until age 6 weeks or study liquid at age 6 weeks or older). It is likely that your baby will receive the liquid before it is known that your infant is infected with HIV.

### **POTENTIAL BENEFITS**

You and your baby may receive no benefit from this study. However, knowledge gained from this study may in the future help others remain HIV uninfected. You and your baby will receive information about your health from the study examinations and laboratory tests.

Being in this study may reduce the chances of your baby getting HIV, but no guarantee can be made. Although all infants will receive nevirapine liquid for the first 6 weeks of life, after age 6 weeks, your baby may be receiving the study liquid called placebo with no medicine in it if her or she was over 6 weeks of age as of 10 August 2007. It is also unknown whether the study liquid with nevirapine will prevent your baby from getting HIV while breastfeeding after the infant is 6 weeks old.

### **REIMBURSEMENT**

At each scheduled visit you will receive [insert site-specific amount of money] to pay for your transport costs.

### **NEW FINDINGS**

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study.

### **REASONS WHY YOU OR YOU BABY MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT**

You or your baby may be removed from the study without your consent for the following reasons:

- the study doctor or study staff decides that continuing in the study would be harmful to you or your baby;
- you are unable to keep appointments or take the study product as instructed;
- the study is cancelled by the sponsor (the US National Institutes of Health), the Ministry of Health in this country, [insert other relevant in-country authorities], the US Food and Drug Administration or the pharmaceutical company supplying the nevirapine.
- the Institutional Review Board or Ethics Committee or Data Safety and Monitoring Board (DSMB) recommend that the study be stopped early. (A DSMB is an outside group of experts who monitor the study.)

If you or your baby withdraws from the study early for any reason, you will be asked to undergo a final assessment including a physical examination and blood draw, if possible.

### **ALTERNATIVES TO PARTICIPATION**

You do not have to continue to be in this study if you do not want to. The only known way to prevent passing HIV from a mother to her baby during breastfeeding is not to breastfeed. The clinic and study staff will explain the risk and benefits of breastfeeding to you and about safe alternatives. You will be provided information about where formula may be obtained. If you decide not to participate in the study, you will not lose the benefits of your standard medical care.

The study staff will also refer you to HIV treatment programs that may become available at this medical facility or in your area. You have a right to consider all options available to you and your baby.

### **COSTS TO YOU**

There is no cost to you for participating in this study. All of study visits and tests and the study drugs for your baby will be provided free of charge.

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.



**CONFIDENTIALITY**

Your and your baby's research records will be confidential to the extent permitted by law. You will be identified by a code. Personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study. Blood and breastmilk collected from mothers, and blood collected from babies as part of this research study will be stored for study tests done later. These specimens will be stored in containers that do not have names on them but rather a code to protect your and your baby's privacy. These samples will be used for tests that are not checking your baby's health. These tests are for learning more about HIV and nevirapine treatment.

Your records may be reviewed by the United States National Institutes of Health (the agency that sponsors this research), the United States Food and Drug Administration, the study monitors, Boehringer Ingelheim (the manufacturer of nevirapine), and [insert name of site IRB].

**RESEARCH-RELATED INJURY**

Medical care will be provided for illness or injury directly related to this study at no cost to you. Care or appropriate referral will be provided for any illness or injury that occurs during the study that is not directly related to the study, but you may have to pay for this care. There are no plans to give you money if there is a research-related complication or injury.

NOTE: You are not giving up any of your legal rights by signing this informed consent document.

**PERSONS TO CONTACT FOR PROBLEMS OR QUESTIONS**

If you ever have questions about this study or in case you are injured as a result of participation in this research study, you should contact (Name of local investigator or study clinician) at (telephone number and physical address). If you ever have questions about your rights as a research subject you may call (name and title of IRB member) at (telephone number and physical address).

## STATEMENT OF CONSENT

I have read the informed consent or had it read and explained to me. I understand the information and I voluntarily agree to continue participating in this study.

\_\_\_\_\_  
Mother's name (print)

\_\_\_\_\_  
Mother's signature or mark

\_\_\_\_\_  
Date

\_\_\_\_\_  
Father's Name (print)  
(If he is reasonably available)

\_\_\_\_\_  
Father's Signature or mark

\_\_\_\_\_  
Date

I observed the informed consent discussion and, to the best of my knowledge, the information provided was complete and accurate. The potential study participant understands the information provided, and she willingly agrees to continue to take part.

\_\_\_\_\_  
Witness' name (print)

\_\_\_\_\_  
Witness' signature

\_\_\_\_\_  
Date

I have fully explained the changes to this study, the procedures, the risk and benefits and other information provided in this consent form to the potential study participant. I have answered all of her questions. To the best of my knowledge, she understands the information provided and willingly agrees to continue to participate in the study.

\_\_\_\_\_  
Investigator's or Designee's  
Name (print)

\_\_\_\_\_  
Investigator's or Designee's Signature

\_\_\_\_\_  
Date

## **APPENDIX II C      SAMPLE CONSENT FOR STORAGE AND FUTURE USE OF BLOOD SAMPLES**

**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 [x.x], Dated [xx xxx xx]**

**Principal Investigators:** [Insert name and contact information for the site PI]

### **INTRODUCTION**

You have decided to take part in the study named above, which is sponsored by the US National Institutes of Health. While you are in this research study, there may be some blood and breast milk samples taken from you and your child that might be useful for future research. This consent form gives you information about the collection, storage and use of your samples. The study staff will talk with you about this information. Please ask if you have any questions. If you agree to the storage of your own and your child's samples, you will be asked to sign this consent form. You will get a copy to keep. You may participate in the follow-up study even if you do not agree to storage of your own and your child's specimens.

### **HOW WILL YOU GET THE SAMPLES FROM ME?**

There will be NO ADDITIONAL samples taken from you for storage. After all the tests are done for this research study, there may be some left over samples of blood and breast milk. If you agree, left over samples will be kept and used for future HIV-related research.

### **HOW WILL YOU USE MY SAMPLES?**

Your own and your child's samples will only be used to look for additional evidence of infection with HIV or other agents, damage caused by infection, or your body's response to infection (such as examining cells, proteins, and other chemicals in your body). Tests may also include examining your genes (DNA), since they might affect your response to disease in important ways. Your genes might make you more or less susceptible to becoming infected, your responses to infection or to treatment stronger or weaker, or make HIV progress more rapidly or slowly. No other kinds of genetic test will be done by anyone on your stored specimens without first explaining the test to you and obtaining your permission.

The researchers do not plan to contact you with any results from tests done on the stored samples. This is because research tests are often done with experimental procedures, so the results of these types of tests are generally not useful for making decisions on managing your health. Should a rare situation come up in which the researchers decide that a specific test result would provide important information for your own or your child's health, the researchers will try to contact you. If you wish to be contacted with this type of test result, you must give the study doctor or nurse any change to your address and/or phone number.

Your samples will not be sold or used directly to produce commercial products. Research studies using your samples will be reviewed by the sponsor of this study (the US National Institutes of Health) and a special committee at the researcher's institution (an Institutional Review Board).

### **HOW LONG WILL YOU KEEP MY SAMPLES?**

There is no time limit on how long your samples will be stored.

### **HOW WILL MY SAMPLES BE STORED?**

Your samples will be stored at special facilities that are designed to store samples safely and securely. The storage facilities are designed so that only approved researchers will have access to the samples. Some employees of the storage facilities will need to have some access to your samples in order to store them and to keep track of where they are, but these people will not have information that directly identifies you.

### **DOES STORAGE OF MY SAMPLES BENEFIT ME?**

There are no direct benefits to you. The benefit of doing research on stored samples includes learning more about HIV infection.

### **WHAT ARE THE RISKS?**

There are few risks related to storing your samples. When tests are done on the stored samples there is a small but possible risk to your privacy. It is possible that if others found out information about you that is learned from tests (such as information about your genes) it could cause you problems with your family (having a family member learn about a disease that may be passed on in families or learning who is the true parent of a child) or problems getting a job.

### **WHAT ABOUT CONFIDENTIALITY?**

To keep your information private, your own and your child's samples will be labeled with a code that can only be traced back to this research clinic. Your personal information (name, address, phone number) will be protected by the research clinic. When researchers are given your stored samples to study they will not be given your personal information. The results of future tests will not be included in your health records or the health records of your child. Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

### **WHAT ARE MY RIGHTS?**

Allowing your own and your child's samples to be stored is completely voluntary. You may decide not to have any samples stored other than what is needed to complete this study and still be in this research study or any future study.

If you decide now that your samples can be stored for future research, you may change your mind at any time. You must contact your study doctor or nurse and let them know that you do not want your samples used for future research. Your **samples will then not be used.**

### **WHAT DO I DO IF I HAVE QUESTIONS?**

For questions about the storage of your samples, contact [inset name of site investigator] at [insert telephone number].

If you have questions about your own and your child's rights as research volunteers, contact [insert the name or title of person on the Institutional Review Board] at [insert telephone number].

## STATEMENT OF CONSENT

Please carefully read the statements below or have them read to you and think about your choice. No matter what you decide it will not affect your care.

I agree to have my own and my child's left over blood and breastmilk samples stored and tested for future research related to HIV infection.

\_\_\_\_\_ Yes

\_\_\_\_\_ No

\_\_\_\_\_  
Volunteer's Name (print)

\_\_\_\_\_  
Volunteer's Signature or mark

\_\_\_\_\_  
Date

\_\_\_\_\_  
Father's Name (print)  
*(If he is reasonably available)*

\_\_\_\_\_  
Father's Signature or mark

\_\_\_\_\_  
Date

\_\_\_\_\_  
Witness' Name (print)  
(as appropriate)

\_\_\_\_\_  
Witness' Signature

\_\_\_\_\_  
Date

I have explained the purpose of storing specimens from the study to the volunteer and have answered all of her questions. To the best of my knowledge, she understands the purpose, procedures, risks and benefits.

\_\_\_\_\_  
Printed name of Study Staff  
Conducting Consent Discussion

\_\_\_\_\_  
Study Staff Signature

\_\_\_\_\_  
Date

GRADE 1	GRADE 2	GRADE 3	GRADE 4
<b>CUTANEOUS/SKIN RASH/DERMATITIS</b>			
Erythema, with or without pruritis	<p>A. Diffuse erythematous macular or maculopapular cutaneous eruption or dry desquamation with or without pruritis; OR typical target lesions without blistering, vesicles, or ulcerations in the lesions.</p> <p>B. Urticaria</p>	<p>A. Diffuse erythematous macular or maculopapular cutaneous eruption or moist desquamation with or without pruritis together with any of the following constitutional findings considered related to study drug:</p> <ol style="list-style-type: none"> <li>1. 5 x ULN AST, ALT or 2 x baseline if baseline &gt; ULN.</li> <li>2. Grade 2 fever</li> <li>3. blistering and/or vesiculation of cutaneous eruptions</li> <li>4. any site of mucosal lesions; OR</li> </ol> <p>B. angioedema; OR</p> <p>C. exfoliative dermatitis defined as severe widespread erythema and dry scaling of the skin, with generalized superficial lymphadenopathy, and with other constitutional findings such as fever, weight loss, hypoproteinemia possibly related to study drug; OR</p> <p>D. diffuse rash and serum sickness-like reactions defined as a clinical symptom complex manifested as fever, lymphadenopathy, edema, myalgia, and/or arthralgia; OR</p> <p>E. diffuse cutaneous eruptions, usually starting on the face, trunk or back, often with prodromal symptoms plus one of the following:</p> <ol style="list-style-type: none"> <li>1. cutaneous bullae, sometimes confluent with widespread sheet-like detachment of skin (&lt;10% body surface area) (Nikolski's sign) (SJS)</li> <li>2. two or more anatomically distinct sites of mucosal erosion or ulceration not due to another cause.</li> </ol>	Diffuse cutaneous eruptions, usually starting on the face, trunk or back, often with prodromal symptoms plus cutaneous bullae with widespread sheet-like detachment of skin (>10% of body surface area), (Nikolski's sign), (SJS/Toxic Epidermal Necrolysis (TEN) overlap syndrome; TEN)
<b>MALNUTRITION (FAILURE TO THRIVE)</b>			
UNDERWEIGHT: 60-80% of the 50th percentile expected weight for age AND Edema Absent	MARASMUS: <60% of 50th percentile expected weight for age AND Edema Absent	KWASHIORKAR: 60-80% of the 50th percentile expected weight for age AND Edema Present	MARASMIC-KWASHIORKAR: <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

## APPENDIX IV TOXICITY MANAGEMENT PROCEDURES

All infants, enrolled or randomized, active on open-label or study drug, may have study treatment temporarily held or be discontinued from study treatment according to the guidelines in section 6.2.2 or according to criteria listed in the following table. Management of any adverse event will be according to the best clinical care available and the judgment of the site investigator or designated clinician.

CONDITION	SEVERITY <sup>7</sup>	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT <sup>8</sup>
<b>HEPATIC TOXICITY MANAGEMENT</b>			
Suspected clinical hepatitis <sup>9</sup>	Any Grade	Hold ( <i>regardless of ALT grade</i> )	Observe and evaluate.  If clinical hepatitis is confirmed: Study drug should be permanently discontinued.  If clinical hepatitis is ruled out and ALT is Grade 1 or lower, study drug can be reintroduced after consultation with and permission from the Protocol Safety Review Team.
Asymptomatic ALT	Grade 2	May be continued pending repeat assessment based on the clinician's judgment.	Repeat laboratory assessment as soon as possible, ideally within 72 hours.  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.  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.
Asymptomatic ALT	Grade 3 or 4	Hold	Repeat laboratory assessment as soon as possible, ideally within 72 hours.  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.  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.  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.  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.

<sup>7</sup> See current standard DAIDS Toxicity Tables for Grading the Severity of Adult and Pediatric Adverse Events and Appendix III for grading criteria.

<sup>8</sup> If study drug is stopped due to toxicity, participant should have repeat clinical and laboratory evaluations every 10-14 days, if possible, until toxicity resolves.

<sup>9</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.

CONDITION	SEVERITY <sup>10</sup>	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT <sup>11</sup>
<b>SKIN RASH MANAGEMENT</b>			
Erythema with or without pruritus	Grade 1	May be continued or held pending repeat assessment based on the clinician's judgment.	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.  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.
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 or held pending repeat assessment based on the clinician's judgment.	Same management as per Grade 1.
Urticaria	Grade 2B	Hold	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 a definitive alternative explanation for the rash/skin reaction <u>cannot</u> be determined, study drug should be permanently discontinued.  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.
Grade 3 (A through E) skin rashes		Hold	Same management as for Grade 2B above.
Grade 4 skin rashes		Immediate and permanent discontinuation	
<b>NEUTROPENIA AND ANEMIA MANAGEMENT</b>			
Grade 1 or Grade 2 neutropenia or anemia: regardless of relatedness		Continue study drug	
Grade 3 neutropenia or anemia: possibly related, probably not related or not related		Continue study drug	Repeat assessment within 5-7 days.  If repeat assessment is Grade 2 or less, continue study drug.  If repeat assessment confirms a Grade 3, continue study drug at least until consultation with the Protocol Safety Review Team. The Protocol Safety Review Team will determine the frequency of repeat assessment and provide instructions for further study drug dosing.
Grade 3 neutropenia or anemia: probably related or related; or any Grade 4 neutropenia or anemia that is <u>not</u> immediately life threatening		Hold	Repeat assessment within 5-7 days.  If repeat assessment is Grade 2 or less, study drug may be restarted.  If repeat assessment is Grade 3 or higher, study drug is not to be re-started without consultation with and permission from the Protocol Safety Review Team.
Grade 4 neutropenia or anemia that is immediately life threatening		Immediate and permanent discontinuation	

<sup>10</sup> See current standard DAIDS Toxicity Tables for Grading the Severity of Adult and Pediatric Adverse Events and Appendix III for grading criteria.

<sup>11</sup> If study drug is stopped due to toxicity, participant should have repeat clinical and laboratory evaluations every 10-14 days, if possible, until toxicity resolves.



CONDITION AND SEVERITY <sup>12</sup>	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT <sup>13</sup>
<b>EVENTS OTHER THAN HEPATIC TOXICITY, NEUTROPENIA AND ANEMIA, OR RASH MANAGEMENT</b>		
Any Grade 1 or 2 event other 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 continued or restarted.</p> <p>If repeat assessment confirms Grade 3 toxicity AND no alternative explanations for the abnormality can be determined, hold study drug, obtain ALT measurement, and reassess for up to 21 days (manage ALT levels as per hepatic toxicity management). If Grade 3 or higher toxicity persists at approximately 21 days, study drug should be permanently discontinued.</p> <p>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.</p>
Any Grade 4 event that is <u>not</u> immediately life threatening other than hepatic toxicity or rash	Hold	<p>Repeat assessment as soon as possible, ideally within 72 hours.</p> <p>If repeat assessment is Grade 2 or less, study drug can be reintroduced.</p> <p>If repeat assessment shows Grade 3 or higher toxicity, manage as per Grade 3 toxicity management.</p> <p>If repeat assessment confirms Grade 4 toxicity AND no alternative explanation for the abnormality can be determined, study drug should be permanently discontinued.</p> <p>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.</p>
Any Grade 4 event that is immediately life threatening	Immediate and permanent discontinuation	

<sup>12</sup> See current standard DAIDS Toxicity Tables for Grading the Severity of Adult and Pediatric Adverse Events and Appendix III for grading criteria.

<sup>13</sup> If study drug is stopped due to toxicity, participant should have repeat clinical and laboratory evaluations every 10-14 days, if possible, until toxicity resolves.

**APPENDIX V: HPTN 046 ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS\***

	<b>ADVERSE EVENT</b>	<b>RELATIONSHIP TO OPEN-LABEL NVP AND STUDY PRODUCT</b>	<b>REQUIRED REPORTING DURATION</b>	<b>AE LOG CRF (DataFax to SDMC)</b>	<b>EAE FORM (to DAIDS RCC within 3 business days of site awareness)</b>
<b>SERIOUS ADVERSE EVENTS</b>	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)
<b>NON-SERIOUS ADVERSE EVENTS</b>	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.