

Section 9. Clinical and Counseling Procedures

This section presents information related to the clinical assessments and counseling sessions performed for HPTN 046. The clinical assessments include obtaining medical history and performing physical examinations on mothers and infants. The counseling sessions include infant feeding counseling, pre- and post-test HIV counseling, and study drug adherence counseling. Detailed information on performing laboratory assessments to complement the clinical assessments is provided in Section 10 of this SSP Manual. Detailed information on completing data collection forms associated with these activities is provided in Section 12. Detailed information on reporting of adverse events is provided in Section 11 of this SSP Manual.

9.1 Infant Feeding Options Counseling

Infant feeding counseling begins prior to any study screening and continues through the length of an individual's participation in HPTN 046. Infant feeding counselors should be designated staff members who are not involved in the study informed consent process. Once a woman has consented to participate in the study, all occurrences of infant feeding counseling will be recorded in study source documents.

Prior to obtaining consent, HIV-infected pregnant women will receive counseling on breastfeeding and safe alternatives from designated infant feeding counselors, who have undergone training consistent with WHO and local Ministry of Health (MOH) guidelines. Counselors will provide accurate information and balanced options on infant feeding choices that are acceptable, feasible, affordable, sustainable and safe for each individual. Women will 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. Counselors should encourage women to make an independent decision about infant feeding and should support women in their choices. Women who are interested in formula feeding will be provided with information on any currently available programs through which formula can be obtained. Women who state that they wish to breastfeed will be advised to breastfeed exclusively and will be referred to the study staff to receive information regarding study participation. It is imperative that only HIV-infected women who, after thorough counseling, clearly wish to breastfeed are included in the study. Ideally, each participating mother should be assigned to a single infant feeding counselor who will follow her and her infant throughout the study.

9.2 Initial Maternal Screening Visit

HIV-infected women who have received infant feeding options counseling and who provide written 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. No protocol-specified procedures or assessments can be undertaken until written informed consent is obtained, which begins the actual study screening process. Activities undertaken prior to this are considered 'pre-screening' activities. For most women, the study screening process will take place over two or more visits beginning during the last trimester of pregnancy and will be completed on or before Day 7 after delivery, although the protocol allows for a truncated screening process that could begin at delivery for women who have not presented previously.

The purpose of the screening process is to determine the mother's eligibility based all of the eligibility criteria included in Section 4.1 of the study protocol and to obtain baseline health information on potential study participants. Ascertainment of eligibility based on the following clinical inclusion criteria requires taking a medical history and conducting a physical examination. (See Section 4.7.1 of the SSP for additional mother eligibility criteria.)

- Documented HIV infection as evidenced by at least 1 positive EIA and 1 positive WB, or by at least 1 positive rapid test and 1 positive WB. Documentation of previous testing should include laboratory records from with identifiers linking the woman to the sample, preferably from an HPTN-affiliated laboratory.
- Third trimester of pregnancy or on or before day 7 after delivery as judged by palpation and self-report of last menstrual period.
- No serious medical condition that would interfere with participation in the study (e.g., that would prevent breastfeeding or adherence to the follow-up schedule), as judged by the on-site clinician
- Any medical condition that would make participation in the study unsafe or interfere with interpreting the study data or achieving the study objectives

Documentation to address all of the eligibility criteria, including but not limited to, the clinical eligibility criteria above must be present in the participant record. A blanket statement regarding all such inclusion criteria, such as, “The participant meets all inclusion criteria outlined in the protocol,” is NOT adequate. Appropriate documentation includes, but is not limited to, a signed and dated chart note to address each negative criterion. For example, “Participant does not have any serious medical condition that would interfere with participation in the study” is an acceptable way to document that the criterion has been met.

If at any time during the screening process, the mother is found ineligible for any reason, the screening process should be stopped and no further assessments are to be done.

9.2.1 Pre- and Post-test HIV Counseling

If documented confirmation of a mother’s HIV status is not available, HIV testing is required during screening. Documentation of previous testing should include laboratory records with identifiers clearly linking the woman to the sample, preferably from a HPTN-affiliated laboratory.

Each site is required to develop a local SOP for HIV test counseling. Although these SOPs will be site-specific, they should all contain the following elements:

- Each individual should be provided with information that allows her to decide for herself whether to be tested (informed decision with informed consent)
- The HIV testing procedure should be organized to maximize confidentiality
- Testing should be linked with information and recommendations regarding HIV
- Adequate pre- and post-test counseling should be provided to all individuals being tested
- Disclosing HIV status to others should be discussed with all participants
- The need for additional and appropriate referrals should be addressed where possible

Resources for HIV voluntary counseling and testing (VCT) procedures are listed below:

- “Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings” set forth by the CDC in 2006. This document can be downloaded at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm>.

- “Revised Guidelines for HIV Counseling, Testing, and Referral,” set forth by the CDC in 2001. This document can be downloaded at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5019a1.htm>.
- “HIV Voluntary Counseling and Testing (VCT): A Reference Guide for Counselors and Trainers,” revised by the Institute for HIV/AIDS at Family Health International in January 2004. A copy of this document can be requested from the CORE protocol specialists.

9.2.2 Screening Medical History and Review of Systems (ROS)

During the pre-natal visit and/or during labor and delivery evaluations, a complete medical history will be taken according to standard practice from mothers to determine eligibility and baseline health. At a minimum, it is recommended that the medical history and ROS include:

- Review of medications taken during this pregnancy and/or currently being taken and why
Note: All medications should be recorded on study source documents and should include but not be limited to antibiotics, antifungals, antimicrobial medications, vitamins, and local herbs and preparations.
- Date of last menstrual period
- Number of previous pregnancies; number of abortions/miscarriages; number of live births (including those who died shortly after birth); number of surviving children
- Exposure to nevirapine, AZT, or any other antiretrovirals for PMTCT prophylaxis during a previous pregnancy or for treatment.
- An open-ended question, such as “What kinds of symptoms or health problems are you having today?” Even if the answer is “none”, please complete and document a brief review of systems (below).
- ROS: “Have you noted any change in your appetite or energy? Have you had any episodes of coughing, diarrhea, or fever? Have you noted swelling of your legs and/or ankles? Have you had any headaches?”

For all maternal visits, clinicians should rely on self report, obstetric history and any other medical records that may be available. Questions, answers and the sources of the information should be well documented on study source documents. Some of this information will be used to complete the Mother’s Enrollment DataFax form.

9.2.3 Screening Maternal Physical Exam

During screening in the third trimester of pregnancy and/or during labor/delivery (postpartum) evaluations, a full physical exam will be performed on mothers to determine eligibility and baseline health status. If screening begins prior to labor and delivery, an antenatal obstetric exam will also be conducted. A full physical exam will be performed according to standard procedures but at a minimum is recommended to include assessment and documentation of:

- General status: mood, orientation, pain, hygiene
- Vital signs: weight, respiratory rate, pulse, blood pressure, and temperature
- Skin: rashes, scars, bruising

- Mouth: presence of lesions or exudate
- Pulmonary: observation of character of respirations, auscultation, heart sounds
- Breasts: sores, cracks, discharge, ulcers, inflammation, lumps
- Abdomen: scars; visible fetal movement; height of fundus; lie; presentation; position; FHR x 1 minute; spleen; liver
- Lymph: palpable cervical, axillary and/or inguinal lymph nodes
- Lower extremities: edema (shins, ankles, feet); varicosities

All pertinent exam findings should be recorded on study source documents. Some information obtained during the screening exam will be used to complete the Mother's Enrollment DataFax form.

9.3 Maternal Labor/Delivery (Postpartum) Screening Evaluations

The maternal labor/delivery eligibility evaluations should be completed as close to delivery as possible but on or before Day 7 after delivery (day of birth=Day 0). If a potentially eligible woman presents for the first time postpartum (i.e. has not begun the screening process before delivery), evaluations are combined as specified in Section 5.1.2 of the study protocol and below.

Maternal medical history and physical examination should provide evidence of the mother's eligibility based on the clinical inclusion criteria as described in section 9.2.

9.3.1 Postpartum Infant Feeding Counseling

Infant feeding counseling should be repeated prior to enrollment to ensure that mothers still intend and are able to breastfeed. The counseling should include a review of the benefits of breastfeeding, the risk of HIV transmission through breastfeeding, and the risks and possible advantages associated with other methods of infant feeding. Counselors will continue to recommend that women breastfeed exclusively if breastfeeding continues to be the mother's intended feeding method.

9.3.2 Postpartum Maternal Medical History and Review of Systems

If a woman has not begun screening prior to delivery, the clinical and laboratory evaluations for the pre-natal screening visit and labor/delivery (postpartum) visit can be combined.

Following labor and delivery, the mother's medical history (as described in section 9.2.2) should be obtained with additional focus on obstetric history and labor and delivery. In addition, medical records should be reviewed for details of labor and delivery. Such information should be ascertained regardless of whether the woman delivered at the study clinic or at another facility. For all maternal visits, clinicians should rely on their own assessment, maternal history and any other medical records that may be available. Questions, answers and the sources of the information should be documented on study source documents. Some information obtained during the medical history will be used to complete the Mother's Enrollment DataFax form. If the mother has taken any antiretroviral medications during this pregnancy for any reason or is currently taking any antiretroviral medications for treatment or for PMTCT (including nevirapine per standard of care), or if she has taken nevirapine for PMTCT in previous pregnancies, this

information must be recorded in the source documents. Information on antiretrovirals other than nevirapine for PMTCT will also be recorded on the Mother's Antiretroviral Medication Log DataFax form. Nevirapine taken during this or previous pregnancies for PMTCT only is to be recorded on the Mother's Enrollment form (in addition to the source documents).

9.3.3 Postpartum Maternal Physical Exam

Prior to day 7 post-delivery, a maternal physical exam will be conducted (as described in Section 9.5.3, below). All aspects of the standard postpartum discharge physical exam should be performed and documented on study source documents. Some information obtained during the physical exam will be used to complete the Mother's Enrollment DataFax form. *Note: If screening begins following labor and delivery, the baseline physical examination and post-delivery physical examination can be combined.*

9.4 Infant Birth Visit/Evaluations for Enrollment

To determine the infant's eligibility for enrollment, s/he will undergo a physical examination, medical history (birth/neonatal history including all medications received or exposed to) and the ability to breastfeed will be ascertained. If at any time during the screening, the infant is found ineligible, the screening process should stop and no further assessments should be done. If the infant is not eligible, the mother is not enrolled. The clinical criteria on which an infant's eligibility for enrollment is based include the following. See Section 4.7.2 for additional infant eligibility criteria.

- 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.)
- Birth weight of at least 2000 g
- Able to breastfeed (e.g., mother and infant alive with no condition apparent that would preclude breastfeeding)
- Absence of the following:
 - 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)
 - 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 on-site clinician

Documentation to address all of the eligibility criteria must be present in the participant record. A blanket statement regarding all inclusion/exclusion criteria, such as, "The participant meets all inclusion criteria outlined in the protocol," is NOT adequate. Appropriate documentation includes, but is not limited to, a

signed and dated chart note to address each negative criterion. For example, “Participant does not have a grade 2B, grade 3 or higher skin rash,” is an acceptable way to document that a criterion has been met.

9.4.1 Infant Birth History

Prior to enrollment, a complete infant birth and postpartum history should be obtained and recorded on study source documents. At a minimum, it is recommended that the history include:

- Time of rupture of membranes and whether spontaneous or artificial
- Where delivery occurred
- Type of delivery
- Time of birth
- Time of delivery of placenta
- Birth weight
- Medications currently being taken and why (other than nevirapine)

Note: All concomitant medications should be recorded on study source documents, including but not limited to antibiotics, antifungals, antimicrobial medications, preventive medications and treatments (e.g., vaccinations and blood transfusions), vitamins, and local herbs and preparations. However, only antibiotics, antifungals, and antimicrobial medications will be transcribed onto the Infant’s Concomitant Medications DataFax form.

For all infant visits, clinicians should rely on their own assessment and the mother’s or caretaker’s report of the infant’s medical well-being as well as any other medical records that may be available. All questions and answers and the sources of the information should be documented on study source documents. Some information obtained during the infant birth history and recorded on study source documents will be used to complete the Infant Birth DataFax form. Antiretroviral medications other than nevirapine for PMTCT given to the infant must be reported on the Infant’s Antiretroviral Medication Log DataFax form.

9.4.2 Infant Birth Physical Exam

To determine the infant’s baseline health status and assess eligibility, a complete infant exam should be performed according to standard site procedures. At a minimum, it is recommended that the infant examination include assessment and documentation of the following:

- General status: APGAR scores
- Vital signs: weight (taken when infant is naked or wearing a dry diaper), crown-heel length, respiratory rate, pulse, axillary temperature
- Skin: general status; rashes, bruising, birthmarks; pallor
- Eyes: sclera; conjunctiva; discharge
- Mouth: presence of lesions or exudates; cleft lip or palate
- Pulmonary: observation of character of respirations, auscultation, heart sounds
- Abdomen: palpable liver or spleen (document how far below the costal margin the spleen and/or liver is palpable)

- External genitalia: male or female
- Extremities: extra digits

Note: Conditions or illnesses, including congenital anomalies, occurring in infants before enrollment are considered pre-existing conditions rather than adverse events.

Information obtained from the baseline infant physical exam should be recorded on study source documents. Some data will be used to complete the Infant Birth and Infant's Randomization DataFax forms.

9.5 Maternal Follow-up Visits

9.5.1 Follow-up Infant Feeding Counseling

Infant feeding counseling should be repeated at every follow-up visit, even after breastfeeding has been terminated. If possible, participants should meet with the same counselor who originally provided counseling at each visit. Prior to breastfeeding termination, counselors should review the importance of exclusive breastfeeding and provide any necessary support or referrals. Counselors will also provide guidance regarding optimal weaning and infant feeding once breastfeeding has been terminated. Weaning will be encouraged at 6 months if it is acceptable, feasible, affordable, sustainable and safe, but individual mothers will ultimately determine the timing of breastfeeding cessation.

Note: Cessation of breastfeeding is defined as the mother's self report of completely stopping all infant exposure to breast milk for 30 days, including exposure for pacification only.

9.5.2 Maternal Interim Medical History and ROS

At each follow-up visit, an interim medical history of the mother will be conducted to obtain updated medical history information about symptoms of HIV infection and treatment including use of antiretroviral medications.

It is not necessary to complete a full medical history at each follow-up visit, rather it is acceptable to inquire about the current status of the mother's health and review and follow up on problems reported at the prior visit. At a minimum, the interim medical history and review of systems (ROS) is recommended to include:

- Review of medications being taken at the last visit and enquiries about any new medications begun since then

Note: All medications, including traditional medicines, should be recorded on study source documents.

- Follow up on any problems identified at the previous visit
- An open-ended question, such as "What kinds of symptoms or health problems have you had since you were last here?"
- A brief review of systems: "Have you noted any change in your appetite or energy? Have you had any episodes of coughing, diarrhea, or fever?"

For all maternal visits, clinicians should rely on maternal self-report and any other medical

records that may be available. All questions and answers and the sources of the information should be well documented on study source documents. Some data from the medical history will be used to complete the Mother's Follow-up Visit, Mother's Antiretroviral Medication Log, and WHO Clinical Staging DataFax forms. As they are not exposed to the study drug, adverse event reporting is not required for mothers.

9.5.3 Maternal Interim Physical Exam

A modified full physical exam will be performed at the designated follow-up visits according to standard procedures. Problems or issues identified during the interim medical history and ROS and at the last follow-up visit may require additional or more detailed assessments, but at a minimum the physical exam is recommended to include assessment and documentation of:

- General status: mood, orientation, pain, hygiene
- Vital signs: weight, respiratory rate, blood pressure, pulse and temperature
- Skin: rashes, scars, bruising
- Mouth: presence of lesions or exudate
- Pulmonary: observation of character of respirations, auscultation, heart sounds
- Breasts: sores, cracks, discharge, ulcers, inflammation, lumps
- Abdomen: palpable liver or spleen (if palpable, document how far below the costal margin the spleen and/or liver can be felt)
- Vulva: tears, discharge, and inflammation
- Lymph: palpable cervical, axillary and/or inguinal lymph nodes

Some information from the study source documentation of the physical exam will be used to complete the Mother's Follow-up Visit and WHO Clinical Staging DataFax forms.

9.5.4 WHO Clinical Staging

At the 6 week, 6 month and 12 month visits, clinicians will complete WHO clinical staging for all mothers. Information for staging will be obtained from the medical history and ROS, physical exam, and laboratory test results from the current and past visits. Definitions of WHO clinical stages are included in Table 9-1, located at the end of this section. Note that once an individual has been assigned to a particular stage, she can never be classified at a lower stage.

Sites should use study source documents to record results of the WHO staging, in addition to completing the WHO Clinical Stage Assessment DataFax form.

9.6 Infant Follow-up Visits

9.6.1 Evaluations for Randomization

All enrolled infants who have initiated the open-label nevirapine (NVP) and have not been discontinued from the medication for toxicity, are still breastfeeding and have not been discontinued from the study are eligible for randomization at 6 weeks (Day 42) if they meet the criteria listed below. 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. Infants will be randomized to

one of two arms, either NVP or NVP placebo and begin study drug dosing at ≥ 43 days of age. Infants must meet the following for randomization:

- HIV-1 DNA PCR negative from a specimen obtained at the 5 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). 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 Grade 2B skin rash (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 tight 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

9.6.2 Infant Follow-up Medical History

At each follow-up visit, a medical history and ROS will be conducted to review the infant's medical history since the last visit and to obtain information about current health, medications used since the last study visit, adverse events, and infant feeding practices. The medical history and review of systems should be performed according to standard procedures, but at a minimum, is recommended to include:

- Review of medications, including traditional medicines, being taken at the last visit and enquiry about any new medications begun since then

Note: All reported concomitant medications should be recorded on study source documents including but not limited to antibiotics, antifungals, antimicrobial medications, preventive medications and treatments (e.g., vaccinations and blood transfusions), vitamins, and local herbs and preparations. However, only antibiotics, antifungals and antimicrobial medications will be transcribed onto the DataFax forms through 8 months of life.

- Review of adherence to study drug: “Sometimes mothers report that they were not able to give the infant all of the doses of the study drug. Were any doses missed? For what reason?”
- Review of infant feeding practices: “Have there been any changes in your baby’s feeding habits? Are you still breastfeeding your infant? What else do you feed your infant in addition to breast milk?”
- Assessment of general health, using an open-ended question such as, “What symptoms or health problems has your infant had or is she/he having since you were last here?”
- A brief review of systems: “Have you noted any change in your baby’s appetite or activity? Has your baby had any episodes of coughing, diarrhea, or fever? Have you seen any signs of rash?”
- Follow up on any problems identified at the previous visit

If the mother answers yes to any of these or other questions, she should be asked follow-up questions for more information about duration, type, etc. Problems or issues identified during the interim medical history and ROS may require additional or more detailed assessments. For all illnesses/adverse events reported, sufficient detail must be obtained to allow for severity grading according the DAIDS Toxicity Tables, as well as details such as onset, duration, current status, etc.

For all infant visits, clinicians should rely on his or her own assessment, the mother’s or caretaker’s report of the infant’s medical well-being as well as any other medical records that may be available. Questions, answers and sources of the information should be well documented on study source documents. Some data will be used to complete the Infant’s Follow-up Visit DataFax form, and the Infant’s Antiretroviral Medication Log, Adverse Experience Log, and Concomitant Medications Log DataFax forms, if necessary.

9.6.3 Infant Follow-up Physical Exam

A complete physical exam should be performed at all infant follow-up visits according to standard site procedures. At a minimum, it is recommended that the infant follow-up exam include assessment and documentation of the following:

- General status: alertness, tone
- Vital signs: weight (taken when infant is naked or wearing a dry diaper), crown-heel length and head circumference, respiratory rate, pulse, axillary temperature
- Skin: rashes, bruising, birthmarks, pallor, scarring
- Ears: tenderness, redness or discharge
- Mouth: presence of lesions or exudate
- Pulmonary: observation of character of respirations, auscultation, heart sounds

- Abdomen: palpable liver or spleen (document how far below the costal margin the spleen and/or liver is palpable)
- Lymph: palpable cervical, axillary and/or inguinal lymph nodes
- External genitalia: presence of rash or discharge
- Assessment of any conditions identified in preceding visits

Information obtained from the interim physical exam should be recorded on study source documents. Some information will be used to complete the Infant Follow-up Visit DataFax form and Infant's Adverse Experience Log if necessary. For all illnesses/adverse events reported, sufficient detail must be obtained to allow for severity grading according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Appendix E of this SSP Manual) and the Supplemental Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis, Malnutrition and Fever (Appendix III of the study protocol and Appendix F of this SSP Manual), as well as details such as onset, duration, current status, etc.

9.7 Definitions of Exam Findings/Diagnoses Identified on DataFax Forms

The HPTN 046 Infant Birth, Infant's Follow-up Visit, and Mother's Follow-up Visit DataFax forms identify several exam findings and diagnoses that will be recorded for data analysis. Specified below in Sections 9.7.1 and 9.7.2 is a list of the relevant exam findings/diagnoses and definitions of each (*Note: most descriptions for infants are from "Nelson Textbook of Pediatrics"*). Although their definitions are included in this list, the following typical childhood illnesses will be recorded in the study source records and captured in the study database as interim medical history or physical exam findings, but will not be reported separately in the infant's Adverse Experience Log CRF:

- diaper rash
- otitis media
- afebrile upper and lower tract infections including bronchiolitis

Additionally, 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.

9.7.1 Infant Conditions

- Jaundice – clinical presentation is dependent on etiology: if due to deposition of indirect bilirubin, will present as yellow or orange tint to the skin and sclera; if due to obstruction (direct bilirubin) will present as a greenish or muddy yellow tint to skin and sclera. Infant may be lethargic and feeding poorly. Intensity of clinical presentation are not dependable surrogate markers of degree of jaundice; bilirubin determinations should be done.
- Oral thrush – diagnosed by the appearance of white patches or plaques covering all or part of the oropharyngeal mucosa, by the microscopic appearance of yeast in an uncultured specimen scraped from the oral mucosa, or a positive culture; removal of plaques reveals inflamed tissue and bleeding.
- Congenital anomaly – an abnormality acquired *in utero* and existing from the time of

birth, although diagnosis of the disorder may occur after the immediate postnatal period (for example, congenital heart disease or pyloric stenosis).

- Hepatomegaly – palpable liver greater than 2 cm below right costal margin.
- Splenomegaly – palpable spleen greater than 1 cm below left costal margin.
- Neonatal sepsis – initial signs may be subtle and limited to reports from mother that infant feeding or behavior has changed. Common manifestations of neonatal sepsis are temperature instability, jaundice, respiratory distress, hepatomegaly, abdominal distention, anorexia, vomiting, poor feeding, and lethargy. Blood cultures should be obtained when possible; bacterial blood culture is usually positive (please specify organism).
- Transient tachypnea – characterized by early onset of tachypnea following delivery; typically resolves within 72 hours; sometimes associated with retractions, expiratory grunting, nasal flaring, or cyanosis; usually no rales or rhonchi noted on auscultation. CXR typically shows prominent pulmonary vasculature, fluid lines in the fissures, hyperinflation, flat diaphragms, and occasionally pleural fluid. Noninfectious etiology, syndrome is believed to be secondary to slow absorption of fetal lung fluid.
- Meconium aspiration – occurs in the presence of meconium stained liquor, infants are frequently meconium stained and depressed and require resuscitation at birth; associated with poor gas exchange in lungs and with a chemical pneumonitis and abnormal CXR, often including pulmonary infiltrates. Depending on the degree of aspiration, infants may develop tachypnea, retractions, grunting and cyanosis.
- Conjunctivitis – ranges from mild symptoms such as those associated with viral conjunctivitis (watery discharge) to moderate symptoms such as those associated with seasonal conjunctivitis (pruritis, tearing and conjunctival edema) to severe symptoms such as those associated with acute purulent conjunctivitis (generalized hyperemia, edema, mucopurulent exudates with varying degrees of discomfort).
 - Ophthalmia neonatorum – acute conjunctivitis in the newborn, usually due to gonococcal or chlamydia infections, characterized by profuse discharge with marked edema and hyperemia of the eyelids and conjunctiva.
- Skin abnormality:
 - Milia – firm pearly opalescent papules, 1-2 mm in diameter. Most frequently scattered over the face and gingivae and on the midline of the palate.
 - Newborn peeling skin – peeling, parchment-like skin most common with post-term infants.
 - Erythema toxicum – benign condition in up to 50% of normal newborns characterized by an evanescent eruption with firm, yellow-white, 1-2 mm papules or pustules surrounded by reddened skin; may be present for a few hours to days. Spotty erythema may be the only presentation. Distribution may be sparse or numerous; clustered in several sites or widely dispersed over much of the body. Palms and soles are almost always spared. Eosinophils present in aspirate of lesions on skin scraping.

- Transient pustular melanosis – characterized by 3 types of lesions: 1) evanescent superficial pustules; 2) ruptured pustules with a fine encircling scale with or without a central hyperpigmented papule; and 3) hyperpigmented papules. Present at birth; distribution may vary; palms and soles may be affected.
 - Heat rash (miliaria) – two main types: 1) miliaria crystalline lesions are superficial and non-inflammatory; the tiny clear vesicles rupture easily; distribution is generalized; 2) miliaria rubra is characterized by papulovesicles with intense erythema; lesions are usually located in sites of occlusion or flexural areas.
 - Diaper (napkin) rash – red popular rash confined in distribution to the area of the nappy; often notable in skin folds; satellite lesions may occur if the infant is infected with thrush or bacteria.
 - Non-specific dermatitis – any dermatitis not otherwise described and for which there is no diagnosis.
 - Birthmark – a circumscribed blemish or spot on the skin of congenital origin; includes hemangioma, unless first apparent after randomization, in which case, include as skin abnormality.
 - Skin infection – may range from superinfected superficial abrasion characterized by erythema, with crusty or pustular discharge to generalized exfoliation with fever. This category should be used for various conditions with a specific diagnosis such as impetigo, scalded skin syndrome, and scabies, as well as those for which a definitive diagnosis does not exist. If a diagnosis exists, it should be specified.
 - Other skin condition – any other skin condition not otherwise described including eczema or atopic dermatitis, insect bites, and drug rashes such as Stevens-Johnson Syndrome. If a diagnosis exists, it should be specified.
- Failure to thrive – failure to gain weight or grow at the expected rate based on consecutive weight and height measurements at the same site, documenting measurements from a child who downwardly crosses two major percentile lines on a standard growth chart, or who is less than the 5th percentile and fails to parallel the growth curve at the 5th percentile.
 - Generalized lymphadenopathy – lymph nodes larger than 1.5 cm palpable in more than one site (cervical, axillary, inguinal, supraclavicular).
 - Otitis Media – reddened tympanic membrane, often retracted (with or without fluid level visible) or ruptured (drainage may have been reported or may still be visible in the canal); often accompanied by generalized irritability with or without fever; diagnosed by physical exam or confirmed by tympanocentesis or positive test for specific organism.
 - Afebrile upper or lower respiratory tract infection (including bronchiolitis) – early symptoms are serous nasal discharge, sneezing, diminished appetite; respiratory distress is characterized by paroxysmal wheezy cough, dyspnea, increased respiratory rate and irritability; occurs in the absence of fever (temperature less than 37.7°C or 99.9°F).

9.7.2 Maternal Conditions

- Generalized wasting – profound involuntary loss of at least 10% of baseline body weight and loss of lean and fat mass plus either chronic diarrhea (at least two loose stools per

days for 30 days or more) or chronic weakness and documented fever (for 30 days or more, intermittent or constant) in the absence of a concurrent illness or condition other than HIV infections that could explain the findings (e.g., cancer, tuberculosis, cryptosporidiosis, or other specific enteritis).

- Generalized lymphadenopathy – lymph nodes larger than 1.5 cm palpable in more than one site (cervical, axillary, inguinal, supraclavicular).
- Kaposi’s sarcoma – includes a wide range of clinical manifestations; usually presents initially as violaceous skin lesions, but oral, visceral, or nodal KS may occur. Usually manifests dermatologically as pigmented macules, plaques, papules, or nodules ranging in size from a few millimeters to large confluent areas many centimeters in diameter and in color from pink, to red or purple, or dark brown or black. Proven by microscopy.
- Hepatomegaly – palpable liver.
- Splenomegaly – palpable spleen.
- Pneumonia – clinical presentation may include congestion, cough, shortness of breath, rapid heart rate and breathing, fever, muscle stiffness, chest pain, and the production of purulent or bloody sputum; possible confirmation by chest radiograph temporally consistent with diagnosis, or proven by culture or other specific assay on blood/biopsy/tissue/bronchoalveolar lavage.
- Other respiratory infection – infections of nonspecific etiologies and/or known conditions including tuberculosis and viral LRI. TB is characterized by a chronic cough and failure to respond to conventional antibiotic therapy, significant weight loss, fever and night sweats, often with a sputum positive close contact. Diagnosis based on sputa, radiograph and clinical course. If a diagnosis is present, it should be specified on DataFax forms.

9.8 Open-Label NVP and Study Drug Adherence Counseling

All women enrolled in the study will be given instructions about study product dosing and will receive adherence counseling at each follow up visit. Adherence assessments will be conducted via maternal interview at all follow-up visits while the infant is on either open-label NVP or study drug and must be completed before adherence counseling is provided. Ideally, someone other than the adherence counselor will conduct the adherence assessment to avoid biasing a mother’s responses. Counseling may include the following elements:

- Definition of and education about the importance of open-label NVP or study drug adherence
- Careful review of dosing amounts by age and frequency of dosing
- Discussion of barriers to adherence and brainstorming about plans to overcome anticipated obstacles
- Discussion of social support and privacy

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.

9.9 Toxicity Grading and Management

Sites should designate an individual clinician who will be responsible for overseeing the severity grading and management of adverse events occurring in children through 18 months of age. This individual will also be responsible for deciding when to remove infants from the open-label NVP or the study drug in consultation with the Protocol Safety Review Team (PSRT) as appropriate. See Appendix G of this SSP Manual for PSRT procedures. Severity of AEs will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (included as Appendix E of this SSP Manual). Cutaneous/Skin Rash/Dermatitis, Malnutrition and Fever AEs will be graded according to the Supplemental Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis, Malnutrition and Fever (included as Appendix F of this SSP Manual). Adverse events relative to open-label NVP or study drug dosing will be managed according to the HPTN 046 Toxicity Management Procedures Table (included as Appendix H). See Section 11 for more information about reporting and management of adverse events.

9.10 Access to HIV-Related Care

All HIV-infected participants – mothers and infants identified during the course of the study – should be actively referred to available sources of medical and psychosocial care and treatment. Sites should establish formal referral mechanisms or agreements with available programs and be familiar with their requirements or criteria for acceptance of new patients so that appropriate referral can be provided depending on the study participant’s disease stage or other locally applied criteria.

Clinical care provided to HIV-infected mothers and infants will 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. The mothers or physical caretakers of all infants determined to be HIV-infected will be offered cotrimoxazole prophylaxis to prevent pneumocystis pneumonia and bacterial infections. All participants who require admission to the hospital should receive close monitoring and follow-up. 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.

Table 9-1: WHO Disease Staging System for HIV Infection and Disease in Adults and Adolescents

<p>Clinical Stage I</p> <ul style="list-style-type: none"><input type="checkbox"/> Asymptomatic<input type="checkbox"/> Persistent generalized lymphadenopathy
<p>Clinical Stage II</p> <ul style="list-style-type: none"><input type="checkbox"/> Unexplained moderate weight loss (<10% of presumed or measured body weight)¹<input type="checkbox"/> Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, and pharyngitis)<input type="checkbox"/> Herpes zoster<input type="checkbox"/> Angular cheilitis<input type="checkbox"/> Recurrent oral ulcerations<input type="checkbox"/> Papular pruritic eruptions<input type="checkbox"/> Seborrheic dermatitis<input type="checkbox"/> Fungal nail infections
<p>Clinical Stage III</p> <ul style="list-style-type: none"><input type="checkbox"/> Unexplained severe weight loss (>10% of presumed or measured body weight)¹<input type="checkbox"/> Unexplained chronic diarrhoea for longer than one month<input type="checkbox"/> Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)<input type="checkbox"/> Persistent oral candidiasis (thrush)<input type="checkbox"/> Oral hairy leukoplakia<input type="checkbox"/> Pulmonary tuberculosis<input type="checkbox"/> Severe bacterial infections (i.e. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, or bacteraemia)<input type="checkbox"/> Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis<input type="checkbox"/> Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 10⁹ per litre) and/or chronic thrombocytopaenia (<50 x 10⁹ per litre)
<p>Clinical Stage IV</p> <ul style="list-style-type: none"><input type="checkbox"/> HIV wasting syndrome<input type="checkbox"/> Pneumocystis pneumonia<input type="checkbox"/> Recurrent severe bacterial pneumonia<input type="checkbox"/> Chronic herpes simplex infection (orolabial, genital, or anorectal of more than one month's duration or visceral at any site)<input type="checkbox"/> Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)<input type="checkbox"/> Extrapulmonary tuberculosis<input type="checkbox"/> Kaposi's sarcoma<input type="checkbox"/> Cytomegalovirus infection (retinitis or infection of other organs)<input type="checkbox"/> Central nervous system toxoplasmosis<input type="checkbox"/> HIV encephalopathy<input type="checkbox"/> Extrapulmonary cryptococcosis including meningitis<input type="checkbox"/> Disseminated non-tuberculous mycobacterial infection<input type="checkbox"/> Progressive multifocal leukoencephalopathy<input type="checkbox"/> Chronic cryptosporidiosis<input type="checkbox"/> Disseminated mycosis (extrapulmonary histoplasmosis or coccidiomycosis)<input type="checkbox"/> Recurrent septicaemia (including non-typhoid <i>Salmonella</i>)<input type="checkbox"/> Lymphoma (cerebral or B-cell non-Hodgkin)<input type="checkbox"/> Invasive cervical carcinoma<input type="checkbox"/> Atypical disseminated leishmaniasis<input type="checkbox"/> Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy<input type="checkbox"/> Chronic isosporiasis

Note: both definitive and presumptive diagnoses are acceptable.

1. Unexplained refers to where the condition is not explained by other causes