

## Section 9. Clinical and Counseling Procedures

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This section presents information on HPTN 057 clinical assessments and counseling sessions. The clinical assessments include obtaining medical history, performing physical examinations on mothers and infants, and taking x-rays of the infant thoracic spine and left wrist at 3 days +/- 2 days and at 3 months (Cohorts 1 – 3 only). Section 10 of this manual contains detailed information on performing laboratory assessments associated with the clinical assessments. Section 11 provides detailed information on the reporting of adverse events (AEs). Instructions on completing data collection forms for clinical and counseling procedures are in Section 12

### 9.1 Initial Maternal Screening Visit (anytime during pregnancy; ideally in the last trimester)

HIV-infected women who provide written informed consent may be screened for the study at any time during pregnancy, but ideally during the third trimester of pregnancy. No protocol-specified screening procedures or assessments can be undertaken until written informed consent for screening is obtained. Once informed consent for screening has been obtained, the study screening process can begin. Activities undertaken prior to this are considered ‘pre-screening’ activities. Since certain evaluations must be done at or after 34 weeks gestation, women who present prior to 34 weeks will be screened in two visits. Women who present at or after 34 weeks gestation can have all screening procedures completed in one visit.

The purpose of the screening process is to determine the mother’s eligibility based on the eligibility criteria included in Sections 3.1 and 3.2 of the study protocol and to obtain baseline health information on potential study participants. Ascertainment of eligibility based on the following inclusion criteria requires taking a medical history and conducting a physical examination.

- $\geq 18$  years of age
- Documented HIV infection as evidenced by a Western Blot or IFA confirmed HIV positive result  
Documentation of previous testing should include laboratory records with identifiers linking the woman to the sample, and should have been reported during a time that the reporting lab has demonstrated proficiency in HIV testing as defined by the Network Lab
- Willingness to deliver at the study site
- Willingness to be admitted to and remain in the delivery facility through Day 3 postpartum (Cohort 1) or through Day 7 postpartum (Cohorts 2, 3 and 4)
- No previous treatment with Tenofovir Disoproxil Fumarate (TDF)
- No active serious medical condition or infection that would interfere with participation in the study (chronic malabsorption or diarrhea (defined as chronic diarrhea for at least 1 month), opportunistic infection, or others) 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 (known multiple pregnancy)
- No laboratory evidence of anemia (Hgb < 8 gm/dL), hepatitis (ALT/SGPT > 3 x site upper limit of normal), or renal dysfunction (serum creatinine > 1.5 mg/dL)
- No participation in any other therapeutic or vaccine trial during the current pregnancy
- No use of any of the disallowed medications within two weeks of the anticipated due date (see protocol section 3.2 for the list of specific medications)

Documentation to address all of the eligibility criteria, including but not limited to, the clinical eligibility criteria above must be kept 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 undertaken. Any information related to the mother’s health obtained during the screening process should be provided to her and explained.

### **9.1.1 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 HIV 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 standard operating procedure (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, such as counseling services and treatment
- Adequate pre- and post-test counseling should be provided to all individuals being tested
- Disclosing HIV status and its impact should be discussed with all participants
- The need for additional and appropriate referrals should be addressed where possible

### **9.1.2 Screening Medical History and Review of Systems (ROS)**

During the mother’s screening visit(s), a complete medical history will be taken according to standard practice in order to determine eligibility and baseline health. At a minimum, it is recommended that the medical history and ROS include:

- Review of current medications and/or medications taken during this pregnancy, including the indication for each. (Medications include any investigational agents, blood products, immunoglobins, and immunotherapy agents.)
- Date of last menstrual period
- Number of previous pregnancies; number of abortions/miscarriages; number of births (including stillbirths and those who died shortly after birth); number of surviving children
- Exposure to nevirapine, AZT, or any other antiretrovirals for prevention of mother to child transmission (pMTCT) prophylaxis during a previous pregnancy or for treatment.

*Note: If the mother is currently taking any antiretroviral medications for treatment or for pMTCT (including nevirapine per standard of care), this information must be recorded in the source*

*documents.*

- 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? Have you experienced any vaginal bleeding?”

For all maternal visits, clinicians should rely on participant self report, obstetric history and any other medical records available. Questions, answers and the sources of the information should be well documented on study source documents.

### **9.1.3 Screening Maternal Physical Exam**

A full physical exam will be performed on mothers during the screening and enrollment visits to determine eligibility and baseline health status and to confirm eligibility. The exam should be performed according to standard procedures and at a minimum should include assessment and documentation of:

- General status: mood, orientation, presence of pain, hygiene
- Vital signs: weight, respiratory rate, pulse, blood pressure, and temperature
- Skin: rashes, scars, bruising
- Mouth: presence of lesions or exudate
- Cardiopulmonary: 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 of this information will be used to complete the Mother's Pre-existing Conditions Form (Cohorts 1 and 3 only). See Section 12 for further instructions on case report form (CRF) completion.

## **9.2 Maternal Labor/Delivery Enrollment Evaluation**

Women who have consented for study enrollment and are eligible will be enrolled at the time they present for delivery once an interim medical history and ROS are conducted (Section 9.1.2). In addition, lab results from the previous screening visit should be reviewed to ensure eligibility. If conditions specified as exclusions (Protocol Section 3.2) have emerged since the screening assessment(s), the woman should not be enrolled. If the interim medical history, ROS, and lab results review indicates that the woman is still eligible, proceed with enrollment. See Section 8 of this study-specific procedures manual (SSP) for instructions on prescribing study drug.

*Note: All data must be documented on study source documents as described in Section 9.1.2 regardless of whether the woman is eligible for enrollment. If at screening, a woman is found to have an abnormal but eligible lab value, this must be documented on the Mother's Pre-Existing Conditions CRF. No CRFs should be completed for women not enrolled.*

## **9.3 Maternal Post-Delivery Evaluations**

Women will have post-delivery clinical evaluations (medical history and symptom-directed physical exams) at 24 to 48 hours postpartum; 5 to 7 days postpartum; 6 and 12 weeks postpartum; and 6 and 12 months postpartum.

### **9.3.1 Post-Delivery Maternal Medical History**

For the post-delivery evaluation done at 24-48 hours postpartum, the mother's medical history should be obtained with primary focus on labor and delivery details. In addition, medical records should be reviewed for details of labor and delivery (e.g. time of rupture of membranes and whether spontaneous or artificial). For all follow-up 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.

If the mother reports taking any antiretroviral medications for treatment, this information must be recorded in the source documents, on the Mother's Antiretroviral Medication Log, and on the Concomitant Medications DataFax form. If the mother reports taking any other types of medications, these must also be recorded in the source documents and on the Concomitant Medications DataFax form.

### **9.3.2 Post-Delivery Maternal Symptom Directed Physical Exam**

A modified symptom-directed physical exam will be performed at the designated follow-up visits according to standard procedures. The physical exam should include (at a minimum) 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

- Cardiopulmonary: 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). During the physical exam conducted at 24-48 hours postpartum, assess condition of uterus, quantity and character of lochia, and assess condition of C-section incision (if applicable).
- Vulva: tears, discharge, and inflammation
- Lymph: palpable cervical, axillary and/or inguinal lymph nodes

Problems or issues identified earlier may require additional or more detailed assessments.

#### **9.4 Cohorts 2 and 3 Infant Birth Evaluations Prior to Infant Dosing**

Only infants born to HIV-infected women screened and enrolled in HPTN 057 are eligible for the study. The only exclusion criterion for infants is related to **dosing** of infants in Cohorts 2 and 3. These are:

- Birth weight < 2000 gm
- Severe congenital malformation or other medical condition not compatible with life or that would interfere with study participation or interpretation, as judged by the examining clinician
- Grade 2 or higher serum creatinine level or other Grade 3 or higher toxicity if known prior to dosing. (Note: test results not required prior to dosing initiation.)
- Multiple birth

For Infants enrolled in Cohorts 2 and 3, documentation addressing all dosing eligibility criteria must be in the participant record before the infant can receive study drug. A blanket statement regarding all initial dosing criteria, such as, “The participant meets all dosing eligibility 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 2 or higher serum creatinine level or other Grade 3 or higher toxicity” is an acceptable way to document that a criterion has been met.

*Note: If the infant in Cohort 2 does not receive the first study drug dose, then the mother/infant pair will be terminated from the study and no further assessments will be done. If the mother in Cohort 3 is not dosed with the study drug for any reason, then the infant will not be dosed and the mother infant/pair will be terminated from the study and no further assessments will be done. See Section 5.4 of this manual for documentation requirements.*

##### **9.4.1 Infant Birth History**

The complete infant birth and neonatal history should be evaluated for all infants enrolled in Cohorts 2 and 3 prior to dosing and within 24 hours of birth for infants enrolled in Cohort 1. Information should be recorded on study source documents. This history should include:

- Type of delivery
- Time of birth
- Sex
- Birth weight

- Crown-heel length
- Medications taken and the indication for each

*Note: All concomitant medications received by the infant at any time during birth or during follow-up, including antiretroviral medications, biologics, and blood products, should be recorded on study source documents and Concomitant Medications Log. All antiretroviral medications given for pMTCT should also be recorded on the Infant's Antiretroviral Medication Logs*

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 available medical records. All questions, answers, and the sources of the information should be noted on study source documents.

#### **9.4.2 Infant Birth Physical Exam**

An initial physical examination should be conducted on all infants enrolled in Cohorts 2 and 3 prior to dosing and within 24 hours of birth for infants enrolled in Cohort 1. This physical exam allows site clinicians to determine the infant's baseline health status and assess eligibility. The examination should be conducted 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
- Cardiopulmonary: 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

Information obtained from the baseline infant physical exam should be recorded on study source documents.

*Note: Any Conditions or illnesses, including congenital anomalies and lab abnormalities, occurring in infants in Cohort 2 before receiving TDF are considered pre-existing conditions rather than adverse events and should be recorded on the Pre-Existing Conditions CRF.*

#### **9.5 Infant Follow-up Visits**

Interim histories will be obtained for all infants in all Cohorts at the following time points: 3 and 5-7 days; 6 and 12 weeks; 6, 9 and 12 months. Please see section 9.5.1 for details on the infant follow-up medical history.

Following that, all infants will be examined at 3 and 5-7 days; 6 and 12 weeks; 6, 9 and 12 months. Please see section 9.5.2 for details on the infant follow-up physical examinations.

Laboratory specimens to be obtained are detailed in Section 10. In addition to the laboratory specimens, x-rays of the thoracic spine and left wrist should be done on all infants – regardless of cohort – at 3 days (+/- 2 days) and at 3 months (Visit 6).

### **9.5.1 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, and AEs. The medical history and ROS should be performed according to standard procedures. At a minimum, it should include:

- Review of current and new medications, including traditional (or herbal) medicines and routine immunizations, received since the last visit.
- Assessment of general health, using an open-ended question such as, “What symptoms or health problems has your infant had since you were last here? Is your infant having any symptoms or health problems today?”
- 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 the status of all AEs ongoing at the last visit
- 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 the event onset, duration, type, frequency, compounding or alleviating factors, treatment, etc. Problems or issues identified during the interim medical history and ROS may require additional or more detailed assessments.

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.

### **9.5.2 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.

## 9.6 Definitions of Exam Findings/Diagnoses Identified on DataFax Forms

The HPTN 057 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. The following is a list of the relevant exam findings/diagnoses and definitions of each (*Note: most descriptions from “Nelson Textbook of Pediatrics”*).

### 9.6.1 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 is not a dependable surrogate marker 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, by a positive culture, or when 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 in the source documents and when completing the AE Log CRF).
- 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 with aspiration of amniotic fluid containing meconium into the fetal or newborn trachea in utero or at first breath; 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 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 chlamydial 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. Splotchy 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 crystallina* lesions are superficial and noninflammatory; 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 papular 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.
  - ♦ Skin infection – may range from infected superficial abrasion characterized by erythema, with crusty or pustular discharge to generalized exfoliation with fever. This category should be used for conditions with a specific diagnosis such as impetigo, scalded skin syndrome, and scabies, and 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).

### **9.6.2 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 the AE Log CRF.

## 9.7 Toxicity Grading and Management

Sites should designate clinicians who will be responsible for overseeing the severity grading and management of AEs occurring in mothers and infants for the duration of the study thru 12 months. This person (persons) will also be responsible for deciding when to stop study drug dosing for infants enrolled in Cohorts 2 and 3. Study drug dosing will be permanently discontinued in infants with the following conditions (Protocol Section 4.6.1)

- Grade 2 or higher serum Creatinine (regardless of relationship)
- Any Grade 3 or Grade 4 clinical or laboratory adverse event (regardless of relationship)

All mothers and infants exposed to the study drug will be asked to remain in the study and complete all follow-up as scheduled, even if the study drug regimen is not completed for any reason.

Severity of AEs will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events dated December, 2004 and Clarification dated August 2009 (which can be found at the following website address: <http://rcc.tech-res.com> with the following exception: calcium will be graded using parameters which include correction for albumin, see Section 4.6 of the Study Protocol version 2.0 and Section x.x of this manual for the specific parameters. Malnutrition and Axillary Fever AEs will be graded according to the Supplemental Table for Grading Severity of Malnutrition and Fever (included in Section 4.6 of the Study Protocol and copied below).

Grading of malnutrition (failure to thrive) will follow the scale below:

- Grade 1 - Underweight: 60-80% of the 50th percentile expected weight for age and edema absent
- Grade 2 - Marasmus: <60% of 50th percentile expected weight for age and edema absent
- Grade 3 - Kwashiorkor: 60-80% of the 50th percentile expected weight for age and edema present
- Grade 4 - Marasmic-kwashiorkor: <60% of 50th percentile expected weight for age and edema present

Axillary measured fever will be graded as follows:

- Grade 1: 37.1 - 38.0 °C
- Grade 2: 38.1 - 38.7 °C
- Grade 3: 38.8 - 39.9 °C
- Grade 4: >39.9 °C

AEs deemed definitely, probably, possibly, and probably not related to study drug dosing will be managed according to the HPTN 057 Toxicity Management Procedures (section 11.16). See Protocol Section 4.6 and Section 11 of this SSP manual for more information about reporting and management of AEs.

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

All HIV-infected participants – mothers and infants identified during the course of the study – should be actively referred to medical and psychosocial care and treatment. Sites should establish formal referral mechanisms or agreements with appropriate programs and be familiar with their requirements or criteria for accepting new patients (i.e., participant’s disease stage)

Clinical care provided to HIV-infected mothers and infants will vary by site. At a minimum, mothers and infants will be offered free diagnosis and treatment for infections and illnesses such as malaria and tuberculosis. All participants who require admission to the hospital should receive close monitoring and follow-up.