Section 8. Clinical Considerations

This section presents information on the clinical procedures performed in MTN-015. Further considerations related to participant safety monitoring and reporting are provided in Section 11 of this manual. Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in Section 10. Instructions for completing data collection forms associated with clinical procedures are provided in Section 12.

Several HIV/AIDS clinical management guidance documents are referenced in this section. Copies of these documents were provided to all sites during study-specific training; please contact the MTN-015 management team if assistance is needed to obtain additional copies.

Any questions related to interpretation of clinical examination findings, interpretation of laboratory test results, and/or clinical management of study participants, should be directed to the MTN-015 Clinical Management Group, using the following email address: mtn015ClinMgt@mtnstopshiv.org

8.1 HIV/AIDS Clinical Care and Support

MTN-015 cannot provide clinical care and treatment to study participants for their HIV infection. However, protocol-specified examinations and laboratory tests will provide information upon which appropriate clinical care decisions can be made for participants. In particular, the study will provide routine information on participants' stage of HIV disease, HIV viral load, and CD4+ T cell count. Information on HIV drug resistance may also be provided, depending on the parent protocol. The study also will provide routine information on participants' hematological status, liver function, and kidney function.

Given the above-listed information, study staff will be well positioned to refer participants to non-study HIV care providers when they meet criteria for initiation of antiretroviral therapy (ART), may be experiencing a drug-related toxicity, or may need to consider changing ART regimens due to resistance. Study staff will provide and explain all study examination findings and test results to participants. They also will provide copies of laboratory test result reports to participants and their non-study providers. Study investigators will be available to consult with non-study providers on optimal clinical care and treatment decisions for participants.

When study staff identify a clinical indication for referral to a non-study HIV care provider, they will actively refer participants to available sources of care, treatment, and support in their communities. Referral arrangements and procedures will be specified in site standard operating procedures (SOPs) prior to study initiation and should be reviewed and updated at least once annually, as care and treatment options will likely expand over time.

All referrals will be provided in accordance with site SOPs and will be documented in participant study records. Although study staff cannot ensure access to care, or that study participants will choose to access available care, they will make every effort to do so. At every study visit, study staff will actively follow-up on prior referrals to determine whether the participant sought the care to which she was referred, determine the outcome of the referral, and determine whether additional referrals are needed. Additional counseling will be provided as needed to help ensure the participant receives appropriate care. All follow-up actions, outcomes, counseling, and plans for next steps will be documented in chart notes.

The IoR should routinely review participant study records to ensure that appropriate referrals are made, documented, and followed up in accordance with site SOPs and participants' clinical indications.

8.2 Medical History and HIV/AIDS Clinical Events

8.2.1 Medical History Taking

Participant medical history information is updated at each MTN-015 visit. When ascertaining and documenting medical history information, record symptoms, illnesses, allergies, and surgeries, and include both acute and chronic conditions. Use clinical experience and judgment — together with any advice available from Community Advisory Board members and others — to determine the best phrasing in local languages to elicit complete and accurate history information from participants.

At the Screening and Enrollment visit:

- Prepare a certified copy of the baseline medical history source document maintained in the participant's parent study record and file the copy in the MTN-015 study record.

- Prepare a certified copy of source documentation of the participant's weight at her seroconversion date or closest weight prior to her seroconversion. Her baseline weight is needed to compare and report unexplained weight loss during follow-up as an HIV/AIDS associated event.

- Prepare and file a certified copy of the last interval medical history source document completed for the parent study prior to enrollment in MTN-015. Certified copies of other relevant parent study medical history source documents also may be prepared and filed at the discretion of the IoR or designee.

- Using designated MTN-015 source documents, document the participant's medical history since the last interval history performed for the parent study, taking care to fully capture the participant's current history at time of enrollment in MTN-015.

At each follow-up visit:

- Review medical history source documents completed at previous visits.

- Using designated MTN-015 source documents, ascertain and document the current status of previously reported conditions. When applicable, follow-up on referrals that were provided in response to previously-identified conditions.

- Using designated MTN-015 source documents, ascertain and document any new conditions that have occurred since the last visit. This may be done using open-ended questions such as "Have you had any [other/new] health problems since your last visit?" Given the relative infrequency of MTN-015 study visits, additional probing may be needed to assist participants in recalling history information dating back to her last visit. For example, it may be useful to ask if the participant saw a primary health care provider or traditional healer, visited a clinic or health centre, or was hospitalized since her last visit.

For each condition ascertained through medical history taking, the following data should be source documented: diagnosis or clinical term used to describe the condition, onset date, resolution date. It is not necessary to grade the severity of each condition; however, the condition should be described in sufficient detail to allow for ongoing clinical assessment and monitoring of the participant over time. The IoR or designee should routinely review medical history source documentation to ensure that adequate information and detail are recorded.

The non-DataFax Medical History log form is a recommended source document for recording medical history information. It should be noted, however, that chart notes and other site-specific source documents should be used to further document the details of all conditions recorded on this form.

8.2.2 Documenting HIV/AIDS Clinical Events

A key objective of MTN-015 is to describe the HIV-related and AIDS-defining clinical events that occur among study participants. The terms "HIV-related" and "AIDS-defining" are based on the World Health Organization (WHO) *Case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children* (http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf). "HIV related" conditions correspond to WHO stage II whereas "AIDS-defining" conditions correspond to WHO stages III and IV.

At each MTN-015 visit, study staff must review all available information and determine whether the participant has experienced any HIV-related or AIDS-defining conditions and, if so, document these on the HIV/AIDS Associated Events Log form. Also at each visit, study staff should review and update (if applicable) all previous entries on the HIV/AIDS Associated Events Log form.

In the process of documenting clinical events at each visit, study staff should assess and document the current clinical stage of the participant and her potential need for co-trimoxazole prophylaxis (CTX), initiation or ART, and/or change of ART regimen per current WHO and/or country specific guidelines. Further guidance on use of CTX and ART can be found on the following WHO webpage: http://www.who.int/hiv/pub/en/

Whenever a potential need for CTX, ART initiation, or change of ART regimen is identified, study staff will actively refer participants to non-study HIV care providers and/or other available source of care and treatment in their communities. To facilitate and support the referrals, study staff will also provide participants with copies of study documentation indicating their current clinical status and stage. The IoR or other study clinician may contact relevant non-study providers to discuss optimal clinical care and treatment for participants. All referrals and provider contacts will be fully documented in participant study records.

8.3 Ascertainment of Concomitant Medications / Antiretroviral Therapy Treatment Records

Concomitant medication information is updated at each MTN-015 visit. For purposes of this study, medications include all of the following, regardless of route of administration:

- Prescription and "over-the counter" medications and preparations
- Preventive medications (e.g., vaccinations)
- Vitamins and other nutritional supplements

- Herbal, naturopathic, and traditional preparations
- Recreational drugs

Although all medications used by study participants must be source documented in MTN-015 study records, only a subset of medications are recorded on MTN-015 case report forms. These are:

- Antiretroviral medications, which are recorded on the Antiretroviral Treatment Regimen Log form
- Medications taken for opportunistic infection prophylaxis, which are recorded on the Non-ART Concomitant Medications Log form
- Hormonal contraceptives, which are recorded on the Non-ART Concomitant Medications Log form
- Single-dose nevirapine used for prevention of mother to child transmission of HIV, which is recorded on the Non-ART Concomitant Medications Log form

The Antiretroviral Treatment Regimen Log form and the Non-ART Concomitant Medications Log form are recommended source documents for recording the above listed medications. For all other medications, the non-DataFax Concomitant Medications Log is the recommended source document. Alternatively, all medications may be source documented on the non-DataFax Concomitant Medications Log and data required to complete the Antiretroviral Treatment Regimen Log form and the Non-ART Concomitant Medications Log form may be transcribed onto these forms.

At each visit:

- Review concomitant medication source documents completed at previous visits.

- Actively inquire as to whether the participant is still taking each previously recorded medication, at the same dose and frequency, and record all updates.

- Actively inquire as to whether the participant has begun taking any new medications since her last visit and record all new medications.

- Record any new medications provided to the participant by study staff.

It is recommended that study staff ascertain participants' medication information in the context of ascertaining their medical history information. In addition to asking open-ended questions to elicit participant report of current medications, study staff should use the information obtained through medical history taking to probe for additional medications that the participant may forget to report. For example, if the participant reports headache as part of her medical history, but does not spontaneously list any medications taken for headache, ask if she took any medications for the headaches. Similarly, if a participant reports taking a medication for a condition that she does not report as part of her medical history, probe for more information about the condition and document the condition on the designated medical history source document.

8.4 Acute Seroconversion Assessment

The acute seroconversion assessment required at the Screening and Enrollment visit is performed by completing the Acute Seroconversion Assessment form and the Seroconversion Symptoms form. These forms require information from the participant's parent study records, as follows:

- The Acute Seroconversion Assessment form requires HIV testing data from the parent study. Prepare certified copies of the relevant parent study source documents and file the copies in the MTN-015 study record. Complete the Acute Seroconversion Assessment form using the certified copies as source.

- The Acute Seroconversion Assessment form also captures historical HIV viral load and CD4+ cell count data, if available. If source documents related to such testing are available in the parent study record, prepare certified copies of the parent study source documents and file the copies in the MTN-015 study record. Complete the Acute Seroconversion Assessment form using the certified copies as source.

- The Seroconversion Symptoms form requires medical history data from the parent study covering the three months prior to seroconversion. Prepare certified copies of the relevant parent study source documents and file the copies in the MTN-015 study record. Complete the Seroconversion Symptoms form using the certified copies as source.

8.5 Physical Examinations: Complete and Symptoms Directed

A **complete physical exam** is required at all scheduled study visits. This exam should include assessments of the following:

- Height
- Weight
- Temperature
- Pulse
- Blood pressure
- General appearance
- Skin
- Head and neck
- Lungs
- Heart
- Abdomen

Additional assessments may be performed at the discretion of the examining clinician. The non-DataFax Physical Exam form is a recommended source document for recording physical exam findings. Supplemental information also may be recorded in chart notes and/or on other site-specific source documents.

NOTE: When assessing and reporting unexplained weight loss as an HIV/AIDS associated event, sites must compare the participant's weight to her baseline weight, the weight at her seroconversion date or closest weight prior to her seroconversion date.

8.6 Gynecologic Exams

Gynecologic exams are performed in MTN-015 to assess for reproductive tract infections (RTIs), including sexually transmitted infections (STIs), and to collect cervical and vaginal specimens for laboratory testing and archive.

Exams should be performed per the Screening and Enrollment visit checklist and the Gynecologic Exam checklist. To ensure the integrity of specimens collected during gynecologic exams, exam procedures must be performed in the order shown on the checklists. Instructions for collecting Cervicovaginal Lavage (CVL) for storage are listed below and see Section 10 of this manual for more detailed instructions related to specimen collection, processing and storage.

Collect the CVL sample for storage as described in the training video available at http://www.mtnstopshiv.org/node/773. Check expiration of sterile saline prior to use and conduct the following procedures:

- Do not collect CVL if there is menstrual blood present.
- Draw 10mL of sterile saline warmed in the water bath into the 20-50 mL syringe.
- Carefully insert tip of syringe into the vagina using care not to touch vaginal walls with syringe. With tip of syringe aimed at the cervix, dispense all 10mL of saline onto the cervix. Gently tilt speculum if necessary to avoid leakage of saline.
- Place tip of a 2mL pipette onto posterior blade of the speculum and draw fluid into pipette, using care not to touch the vagina or cervix.
- Use the 10mL of saline to lavage the cervix, fornices and vaginal walls. Be sure to lavage each sidewall at least twice. Only use the original 10mL of sterile saline. Do not use any additional saline to perform lavage.
- The saline must be in contact with the vaginal vault for at least 1 minute.
- After at least one minute of contact, remove lavage fluid with 20-50mL syringe and sterile tubing or 2ml pipette.
- Save lavage fluid for analysis. Transfer fluid to 20-50mL conical centrifuge tube.
- Sample must be transported to the lab on ice packs quickly enough for processing to be completed within 8 hours.

Pap smears will be performed in MTN-015 at sites with the capacity and expertise to prepare and interpret the smears and provide referrals to appropriate follow-up care to participants with abnormal results. Pap smears should be performed at six-month intervals in the first year after seroconversion, and then annually if the initial tests are negative. When performed, results of pap specimens should be recorded on the Pap Test Result. Sites should follow local standards of care related to the frequency of cervical cancer screening in HIV infected individuals and associated clinical management as specified in site SOPs. For further guidance, refer to *Cervical Cancer Screening for Women Who Attend STD Clinics or Have a History of STDs* (CDC, 2010) and the *2012 Consensus Guidelines for the Management of Women with Abnormal Cervical Cancer Screening Tests* (2012 ASCCP Consensus Guidelines Conference).
The Non-DataFax Pelvic Exam Diagrams form is a recommended source document for recording all exam findings; supplemental information also may be recorded in chart notes and/or on other site-specific source documents. Exam findings are not recorded on case report forms but collection of vaginal swabs and cervicovaginal lavage fluid during exams is documented on the Specimen Storage form.

When vaginal fluid wet mount procedures are required to be performed, the Sexually Transmitted Diseases Results form is the recommended source document for recording vaginal pH and the presence of homogenous vaginal discharge. Unless wet mounts are read in clinic be clinic staff, other wet mount findings should be source documented on designated laboratory source documents and then transcribed onto the Sexually Transmitted Diseases Results form.

8.7 STI/RTI Management

Clinical and laboratory evaluations are performed in MTN-015 to assess for the following STIs/RTIs:

- Bacterial vaginosis (BV)
- Candidiasis
- Chlamydia infection
- Gonorrhea infection
- Syphilis infection
- Trichomoniasis

Signs and symptoms commonly associated with the above-listed infections are presented in Figure 8-1. Infections should be considered "symptomatic" when a participant reports or complains of symptoms associated with the infection. Symptoms should not be confused with "signs" of infection that may be observed during clinical evaluations performed by study staff.

STIs/RTIs will be treated in accordance with current *WHO Guidelines for the Management of Sexually Transmitted Infections* except that asymptomatic candidiasis and asymptomatic BV will not routinely be treated. Current WHO guidelines are available at the following web site:

http://www.who.int/reproductive-health/publications/mngt_stis/guidelines_mngt_stis.pdf

In day-to-day practice, the WHO guidelines — or local site treatment guidelines based on WHO guidelines — should be referenced to obtain complete information on treatment regimens, contraindications, etc. To optimize cure rates, directly observed single dose treatment regimens should be provided whenever possible.

Tests of cure are not required in MTN-015; however, clinical management of syphilis infections should include repeat serology (RPR) at six-month intervals following diagnosis of a new infection to confirm treatment effectiveness. If the RPR titre does not decrease four-fold or revert to seronegative within six months of treatment, treatment should be repeated. Email the MTN-015 Clinical Management Group (mtn015ClinMgt@mtnstopshiv.org) with any questions related to RPR testing to confirm treatment effectiveness, interpretation of unusual syphilis test results, and/or appropriate clinical management of test results.

Figure 8-1
Signs and Symptoms Commonly Associated with STIs/RTIs

STI/RTI	Common Signs and Symptoms
Bacterial vaginosis	Excessive or malodorous discharge is a common finding. Other signs or symptoms include erythema, edema, and pruritis of the external genitalia.
Candidiasis	Clinical presentation includes whitish vaginal discharge and erythema, edema, and pruritis of the external genitalia.
Chlamydia infection	Most infections are asymptomatic, but infection may be accompanied by cervicitis (defined as the presence of endocervical mucopurulent discharge, easily induced cervical bleeding, and/or edematous ectopy).
Genital herpes	Single or multiple vesicles which can appear anywhere on the genitalia. Vesicles spontaneously rupture to form shallow ulcers that may be painful. Lesions spontaneously resolve with minimal scarring.
Gonorrhea infection	Commonly asymptomatic but women may have abnormal vaginal discharge, or dysuria.
Syphilis infection — primary	The classical chancre is a painless indurated ulcer, located at the site of exposure.
Syphilis infection — secondary	Patients may have a highly variable skin rash, mucous patches, condylomata lata (fleshy, moist tissue growths), lymphadenopathy, alopecia, or other signs.
Syphilis infection — latent	Patients are without clinical signs of infection.
Trichomoniasis	Excessive, frothy, diffuse, yellow-green discharge is common, although clinical presentation varies from no signs or symptoms to erythema, edema, and pruritis of the external genitalia. Dysuria and dyspareunia are also frequent. The type of symptoms or signs alone does not distinguish the microbial etiology.

Adapted from: *Contraceptive Technology* (20th Revised Edition, 2011); Chapter 21: Reproductive Tract Infections; Alphabetic Catalog of Reproductive Tract Infections; pages 571-620.

At some study sites, Pap smear results may include notations of findings associated with certain STIs (e.g., trichomoniasis). Because Pap smear methods are not adequately sensitive and specific for STIs, Pap smear findings associated with STIs should not be considered diagnostic of any infections. Rather, such findings should be handled as follows:

- Do not consider STI-related notations on Pap smear result reports when diagnosing STIs or completing the Sexually Transmitted Diseases Results form.

- If protocol-specified STI testing was performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for Pap smear, the results of the protocol-specified testing overrule STI-related findings noted on the Pap smear result report. Provide treatment as needed based on the results of the protocol-specified tests.

- If protocol-specified testing was not performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for the Pap smear, collect specimens for indicated protocol-specified STI testing at the

participant's next study visit after receipt of the Pap test result report. Provide treatment as needed based on the results of the protocol-specified tests. Note that BV and candida do NOT require retesting at the participant's next visit unless she is symptomatic.

8.8 Pregnancy Management

Please refer to the Section 5.6 of this manual for procedural instructions for management of participant pregnancies that may occur during follow-up.

8.9 Critical Laboratory Value Reporting and Management

Hematology, liver function, and renal function testing will be performed routinely throughout the course of MTN-015. CD4+ T cell counts and HIV viral loads also will be routinely tested. For each MTN-015 participant, the IoR or designee is responsible for monitoring these test results over time and for ensuring appropriate clinical management of all results.

- To facilitate the monitoring of hematology, liver function, and renal function test results over time, the severity of these results may be graded per the current DAIDS Toxicity Table (when applicable) and recorded on a flow sheet filed in each participant's study record. Should an updated version of the DAIDS Toxicity Table be issued during MTN-015, sites are advised to follow existing ongoing laboratory abnormalities to resolution based on the toxicity table the condition was originally graded with, then grade all new events moving forward with the most current toxicity table. It is similarly recommended that a flow sheet be used to monitor CD4+ cell counts and HIV viral loads over time. Sample flow sheets that may be adapted for this purpose are provided below.

  All study sites must establish SOPs for reporting and managing critical laboratory values in MTN-015. Critical values are determined locally by site physicians in conjunction with local laboratories performing the testing. Sites may want to consider classifying results with a severity grade of 3 or 4 as critical. Similarly, sites should consider CD4 counts below 250 as critical. Positive STI results may be critical or have other expedited reporting.

  As noted above, the IoR or designee should routinely review MTN-015 participant study records to ensure the adequacy of study documentation and to ensure appropriate management and referrals in response to participants' clinical indications. As part of this quality assurance activity, it is strongly recommend that the IoR or designee review participant CD4+ cell counts and HIV viral loads on a frequent and routine basis, e.g., monthly; other laboratory results also should be routinely reviewed, and all reviews performed by the IoR or designee should be documented in participant study records.

Sample MTN-015 Hematology, Liver Function, and Renal Function Flow Sheet

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Collection Date:												
Visit Code:												
	Result	Grade	Result	Grade	Result	Grade	Result	Grade	Result	Grade	Result	Grade
Hemoglobin												
Red blood cells		NA		NA		NA		NA		NA		NA
MCV		NA		NA		NA		NA		NA		NA
Platelets												
White blood cells												
Neutrophils – abs												
Neutrophils - %		NA		NA		NA		NA		NA		NA
Lymphocytes – abs												
Lymphocytes - %		NA		NA		NA		NA		NA		NA
Monocytes – abs		NA		NA		NA		NA		NA		NA
Monocytes - %		NA		NA		NA		NA		NA		NA
Eosinophils – abs		NA		NA		NA		NA		NA		NA
Eosinophils - %		NA		NA		NA		NA		NA		NA
Basophils- abs		NA		NA		NA		NA		NA		NA
Basophils - %		NA		NA		NA		NA		NA		NA
Total bilirubin												
AST												
ALT												
Alk phos												
Creatinine												

Sample MTN-015 CD4+ Cell Count and HIV Viral Load Flow Sheet

Collection Date	Visit Code	CD4+ Cell Count	HIV Viral Load