

Section 9. Clinical and Counseling Procedures

9.1 Overview of Section 9

This section presents information related to the clinical assessments and counseling sessions performed for HPTN 052. The clinical assessments include obtaining medical history; collecting concomitant medication information; performing physical, genital, and pelvic examinations; collecting circumcision data from male Index Cases and Partners, diagnosing and treating sexually transmitted diseases (STDs), and HIV/AIDS-related opportunistic infections; and reporting adverse experiences. The counseling sessions include pre- and post-test counseling for HIV screening, antiretroviral therapy (ART) adherence counseling, and couples counseling. Detailed information on performing laboratory assessments to complement these clinical assessments is provided in Section 10. Detailed information on completing data collection forms associated with these activities is provided in Section 11.

9.2 Clinical Procedures

9.2.1 Medical History

9.2.1.1 Screening

During the screening visit, a directed medical history will be taken from Index Cases to determine eligibility. Specifically, this directed history should determine the following:

- Documented or suspected acute hepatitis irrespective of AST or ALT values.
- Current or previous AIDS-defining illness as defined in Appendix III of the HPTN 052 Protocol, V3.0.
- Active or previously treated tuberculosis
- Acute therapy for serious medical illnesses
- Recent or anticipated need for radiation therapy or systemic chemotherapy
- Any immunomodulator or other investigational therapy
- Active drug or alcohol use or dependence that could interfere with adherence to study requirements.

- Vomiting or inability to swallow medications due to an active pre-existing conditions that could prevent adequate swallowing and absorption of study medication.
- Allergy/sensitivity to any study drugs or their formulations.
- Pregnancy or currently breast-feeding
- Injection drug use within the past 5 years
- Receipt of an experimental HIV vaccine
- Incarceration in a correctional facility, prison, jail, or medical facility for psychiatric or physical (*e.g.*, infectious disease) illnesses.
- Any medical condition that would make participation in the study unsafe or interfere with interpreting the study data or achieving the study objectives.

9.2.1.2 Enrollment

During the enrollment visit, a complete medical history will be taken for both the Index Case and the Partner. All ongoing conditions identified before or at the enrollment visit, including abnormal lab results from blood draw at the enrollment visit, should be documented on the DataFax Index Pre-Existing Conditions form and graded in the source documentation. Recurring or chronic conditions are considered ongoing whether or not they are active at baseline. In particular, sites should check for the medical conditions listed in Appendix IV per LoA#1 to V. 3.0 of the protocol.

9.2.2 Concomitant Medications

The HPTN 052 protocol requires documentation of all medications taken by the Index Case beginning at enrollment and continuing throughout follow-up. For purposes of this study, medications include prescription and “over-the-counter” medications and preparations, regardless of route of administration. Vitamins and other nutritional supplements should be included, as well as herbal and naturopathic preparations.

Starting with the enrollment visit, the DataFax Index Concomitant Medications Log form is used to collect information on participant’s use of medications other than ART. Concomitant medications should be documented for all Index Cases, whether or not they are being treated with ART.

9.2.2.1 Screening

During the screening visit, it should be determined whether HIV-infected individuals have current or previous use of any HIV ART. In general, past or present use of HIV ART is an exclusion criterion for the study, except in the following cases:

- The use of short-course ART during pregnancy to prevent vertical transmission.

Investigators may enroll women who have received ART as part of maternal to child transmission prevention, including 7-day post-partum ART used for the prevention of NVP resistance, regardless of the precise duration or type of therapy as long as no other exclusion criteria are in place (such as concurrent therapy). No other post-partum ART exposure will be permitted. Site investigators may use their own discretion for determining the first-line therapy for any woman for whom her pMTCT ART regimen may have put her at risk for resistance (*e.g.*, single dose NVP or less than 6 months since child birth).

- Exposure to ART for any reason other than for the prevention of mother-to-child transmission (MTCT).

Anyone with previous ART exposure that is less than or equal to 2 days using nucleoside analogues, protease inhibitors, or both, may be eligible for the study.

Anyone with additional ART exposure for any reason other than for the prevention of MTCT is not eligible for the study.

During screening, it should also be determined whether a potential Index Case needs to take any of the medications prohibited by the protocol (see Section 4.3.2 of the protocol), as this is an exclusion criteria.

9.2.2.2 Enrollment

It is recommended that study clinicians determine baseline medication information in the context of conducting the baseline medical history. In addition to asking open-ended questions to elicit participant report of current medications, information obtained from the medical history should be used to probe for the use of medication. For example, if a participant reports recurrent headaches as part of his or her history, but does not spontaneously report any headache medication, he or she should be asked if headache medication is being used.

9.2.2.3 Follow-up

During each follow-up visit for the Index Case, retrieve the participant's previously completed DataFax Index Concomitant Medications Log, record any new medications provided to the participant by study staff, and **actively** inquire as to whether the participant is still taking medications listed previously, at the same dose and frequency. Also **actively** inquire as to whether the participant has begun taking any new medications **since the last study visit when concomitant medication information was collected**. To further probe for updates, if the participant reports any illnesses or symptoms, inquire as to whether any medications were taken in response to these conditions. Add all new information

to the DataFax Index Concomitant Medication Log, using additional form pages as needed.

9.2.3 Physical Examination

9.2.3.1 Complete Physical Examination

A complete physical examination will be conducted for both Index Cases and their Partners during the enrollment visit and will include height, weight, temperature, blood pressure, pulse, and examination of the following body systems and components: HEENT (head, eyes, ears, nose, and throat), neck, lymph nodes, cardiovascular, pulmonary, abdomen, genitourinary (pelvic exam for women, external genital exam for both men and women), skin, neurological, extremities, and mental status. The findings from this exam should be recorded in the participant's charts.

All on-going abnormal findings identified during the physical examination of the Index Case should be documented on the DataFax Index Pre-Existing Conditions form. It is important to grade these preexisting conditions in the source documentation so that AEs can be reported if the severity of the conditions increases.

9.2.3.2 Targeted Physical Examination and Review of Symptoms

A targeted physical examination may be performed every month for Index Cases and on a quarterly basis or in the case of seroconversion for Partners. These follow-up examinations will be driven by signs and symptoms reported by the participant at or since the last visit. All abnormal findings that fit the criteria of an AE of Grade 3 or higher or are an HIV/AIDS associated event in the Index Case should be documented in the DataFax Index Follow-up form. All abnormal findings described in Appendix IV (LoA#1 to V. 3.0) should be documented and reported to the database as described in Section 9.2.12. All signs, symptoms, and diagnoses should be graded in the source documentation and followed until resolution.

9.2.4 Genital and Pelvic Examination

Genital and pelvic examinations will be performed on both Index Cases and their Partners at enrollment, on a yearly basis, and if the Partner seroconverts. The examinations should focus on finding evidence for the presence of sexually transmitted diseases (STDs). As such, all suspected cases of STDs should be confirmed and treated according to the site's national guidelines. In addition, all ulcers should be swabbed (and locations noted) for differential diagnosis by the HPTN Network Laboratory.

9.2.4.1 Procedure for Women

If the woman is menstruating during a visit that requires a pelvic exam, she may return before the next visit during which the exam can be conducted and the samples collected. If this is not possible, the exam and sample collection can be conducted at the next visit. If the samples are still unattainable at this subsequent visit (either within the visit window, at an interim visit, or at the next scheduled visit), study staff should not attempt to collect the samples again until the protocol requires it. Study staff should try to schedule the enrollment visit at a time when the female Index Case is not menstruating as this is a critical baseline measurement that should be collected prior to ART initiation.

- Palpate and examine inguinal area for adenopathy, bubos, or other pathology.
- Visually examine genital and rectal area (skin and mucosal surfaces) for genital ulcers or other abnormalities.
- Take any visit-specific specimens for STD diagnosis from the vaginal walls (after the speculum is inserted).
- Insert speculum into the vagina, clean the cervix and then visually examine it noting mucopus, friability, and ulcers.
- Take any visit-specific specimens for cervical secretions or STD diagnosis from the endocervical canal.
- While slowly withdrawing the speculum, examine the vaginal mucosa for ulcers, discharge, or other abnormalities.
- Conduct a bimanual exam noting cervical motion tenderness, adnexal masses, or tenderness.

Table 9-1 outlines the specimens to collect if clinically indicated.

Table 9-1 STD Diagnoses

Clinical Sign	Specimen
Women and Men	
Inguinal adenopathy or skin rash	<ul style="list-style-type: none"> Blood for syphilis serology**
Genital ulcer	<ul style="list-style-type: none"> Swab base of ulcer for multiplex PCR* Blood for syphilis serology**
Women Only	
Cervicitis	<ul style="list-style-type: none"> GC and CT PCR from cervical discharge**
Vaginal discharge	<ul style="list-style-type: none"> Wet mount (saline and KOH)** Vaginal pH**
Men Only	
Urethral discharge	<ul style="list-style-type: none"> GC and CT PCR from discharge** Gram stain of discharge***

*Required by protocol.

**Required by protocol annually even if participant is asymptomatic.

***Site-dependant procedure; not protocol mandated.

9.2.4.2 Procedure for Men

The genital examination for men should include the following procedures:

- Palpate and examine inguinal area for adenopathy, bubos, or other pathology.
- Visually examine genital and rectal area for genital ulcers or other skin abnormalities
- Examine urethra for signs of urethral discharge.
- Examine scrotum and scrotal contents if patient complains of scrotal pain or swelling.
- Determine circumcision status (for enrollment and annual visits only).

Table 9-1 outlines the specimens to collect if clinically indicated.

9.2.5 Chest X-ray

A chest x-ray is required for each Index Case at the enrollment visit. However, if a chest x-ray was performed during the screening visit, another x-ray at enrollment is not required. This procedure should be conducted and interpreted according to local site SOPs. The resulting film should be maintained as part of the participant's research record.

9.2.6 Specimen Collection

Blood, urine, and genital secretions will be collected for analysis; however, only blood and genital secretions will be saved and placed in long-term storage for future analysis during HPTN 052. Specific instructions for collecting these samples are included in Section 10 of this SSP manual.

9.2.7 Primary HIV Care

Aside from ART, all Index Cases should receive primary HIV care including prophylactic and symptomatic treatment for HIV/AIDS-related opportunistic infections. Each site is required to develop a local SOP indicating the guidelines to be followed for primary HIV care. If available, sites may use their local guidelines; however, the following guidelines may be used or adopted with modifications:

- The current version of **Medical Management of HIV Infection**, John Bartlett and Joel Gallant. This resource is updated on a regular basis and can be ordered from <http://hopkins-aids.edu>. Updates to this publication are also available at the same website.
- **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents - June 18, 2008**. A copy of these recommendations can be downloaded at:
<http://www.aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?MenuItem=Guidelines&Search=Off&GuidelineID=211&ClassID=4>

Other resources that may be useful for HIV primary care include the following:

- **A Guide to Primary Care of People with HIV/AIDS**, 2004 Edition. A copy of these recommendations can be downloaded at:
<ftp://ftp.hrsa.gov/hab/PCARE04.pdf>
- **A Pocket Guide to Adult HIV/AIDS Treatment: A Companion to A Guide to Primary Care of People with HIV/AIDS (February 2006 Edition)**. A copy of these recommendations can be downloaded at:
<http://ask.hrsa.gov/detail.cfm?PubID=HAB00403>
- **Clinical Manual for Management of the HIV-Infected Adult**, July 2007. A copy of these guidelines can be downloaded at: http://aidsetc.org/pdf/AETC-CM_071007.pdf

- **Living well with HIV/AIDS: A Manual on Nutritional Care and Support for People Living with HIV/AIDS**, 2002, Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). This manual is available at: <http://www.fao.org/DOCREP/005/Y4168E/Y4168E00.HTM>.
- African sites are encouraged to follow the WHO/UNAIDS guidelines for the prophylactic use of cotrimoxazole. A copy of these guidelines can be downloaded at: http://data.unaids.org/publications/IRC-pub04/recommendation_en.pdf

9.2.8 ART Management

Study physicians should refer to the protocol, package inserts, and investigator brochures to prescribe and manage toxicities associated with the ART regimens used in the study. Table 9-2 summarizes the recommendations for how to advise study participants who have missed a dose of study drug.

Table 9-2: Instructions for Late or Missed Doses of ART

Drug	Standard Dose	Instructions for Late or Missed Doses	Precautions
Combivir	1 tab bid	Take as soon as possible.	Doubling doses acceptable, but may cause GI upset.
Lamivudine (3TC)	300 mg qd	Take as soon as possible.	Doubling doses acceptable.
Efavirenz (EFV)	600 mg qd	Take as soon as possible.	Daytime dosing acceptable, but may cause increase in CNS side effects. Doubling dose is not recommended as it may increase CNS side effects.
Atazanavir (ATV)	400 mg qd	Take as soon as possible with food.	Doubling dose acceptable.
Didanosine (ddI-EC)	250 mg (<60 kg) or 400 mg (≥60 kg) qd	Take as soon as possible on empty stomach.	Doubling dose is not recommended.
Stavudine (d4T)	30 mg (<60 kg) or 40 mg (≥60 kg) bid	Take as soon as possible.	Doubling dose acceptable.
Nevirapine (NVP)	200 mg bid	Take as soon as possible.	Doubling doses acceptable, but only after 2-week induction phase (200 mg qd) is complete.
Tenofovir (TDF)	300 mg qd	Take as soon as possible.	Doubling doses acceptable.

Drug	Standard Dose	Instructions for Late or Missed Doses	Precautions
Lopinavir/ritonavir (Kaletra/Aluvia, LPV/r):	400/100 mg bid	Take as soon as possible	Doubling doses acceptable, as LPV/r can be given at 800/200 mg qd in PI-naïve patients.
Tenofovir/emtricitabine (Truvada, TDF/FTC)	300/200 mg qd.	Take as soon as possible.	Doubling doses acceptable

9.2.9 Procedures for the Use of ART for nPEP (Non-occupational Post-exposure Prophylaxis)

nPEP is not promoted for use in this study; however, there may be circumstances under which nPEP is necessary. The decision to use nPEP after a condom break or for other episodes of potential sexual exposure to HIV must be based on the clinical judgment of the health provider, independent of the HPTN 052 trial. The decision would be based on the risk of exposure, toxicity and benefit of nPEP (based on animal data), client interest and potential for client adherence for 28 days. If nPEP is selected, study drugs cannot be used for this purpose.

It is not required to consult the CMC to make the decision to initiate nPEP; however, the CMC is always available to answer questions surrounding this situation.

9.2.10 HPTN 052 Clinical Management Committee (CMC)

The purpose of the HPTN 052 Clinical Management Committee (CMC) is to help sites address issues of clinical judgment. The CMC will be made up of 14 to 16 members including the experienced HIV physicians, the protocol chair, the DAIDS medical monitor, a representative from the DAIDS Pharmaceutical Affairs Branch (PAB), the HPTN 052 CRMs, and representation from SCHARP.

Questions to this committee can include, but are not limited to:

- Questions about inclusion and exclusion criteria for particular participants
- Questions about protocol interpretation
- Questions about ART management (*e.g.*, regimen change or toxicity management)
- Questions about primary HIV care
- Questions about the clinical management of co-morbidities
- Questions about the prophylaxis and treatment of OIs
- Questions about AE management
- Questions about grading and reporting AEs and EAEs

PLEASE DO NOT email questions about protocol requirements or interpretation, data management, laboratory issues, or study operations to the CMC. Such questions should be sent to 052MGMT@HPTN.org and they will be addressed by SCHARP, the HPTN NL, or the HPTN CORE, respectively.

Two physicians (1 U.S. and 1 international) will be “on-call” for 2-week shifts. During that time, these two committee members will be responsible for soliciting input and responding to site queries within a 24-hour time period. One of these physicians will be the primary responder; the other will be the secondary responder. It is the ultimate responsibility of the primary responder to respond to all email queries to the CMC.

Anyone is welcome and encouraged to send questions to the CMC. The HPTN CORE will maintain a web page summarizing the questions and answers addressed by the committee. The CMC may have conference calls as necessary to discuss ongoing case management and to allow site PIs to interact more directly with the committee.

Questions to the committee should be emailed to: 052CMC@hptn.org.

9.2.11 HPTN 052 Protocol Safety Review Team (PSRT)

9.2.11.1 Roles and Responsibilities of the PSRT

Per the HPTN 052 protocol, the role and responsibility of the Protocol Safety Review Team (PSRT) is to conduct regular reviews of standardized study safety data reports (protocol Section 6.0). Once the HPTN Statistical and Data Management Center (SDMC) begins receiving study follow-up safety data, the PSRT will convene via monthly conference calls. The frequency of calls may be adjusted throughout the period of study implementation as agreed upon by the PSRT. Should any safety concerns be identified by the PSRT, they will be relayed to the DAIDS Vaccine and Prevention Data and Safety Monitoring Board.

The responsibilities of the PSRT Chair will include:

- Ongoing review of safety data sent to the Chair by the SDMC.
- Work with the SDMC Clinical Affairs staff querying sites on questions arising from the ongoing safety reviews.
- Lead monthly PSRT calls including summarizing safety data, noting any points of concern
- Working with the SDMC Clinical Affairs and Programming staff to ensure that the PSRT reports meet PSRT reviewer needs.

The responsibility of the DAIDS Medical Officers will include the provision of a written or oral report on the monthly PSRT calls summarizing all new EAEs received from sites since the last PSRT call.

The HPTN CORE is responsible for setting up PSRT calls and/or meetings and minutes.

9.2.11.2 PSRT Composition

The following individuals will serve as active members of the HPTN 052 PSRT:

PSRT Chair:	Claude Drobnes
Protocol Chair:	Myron S. Cohen
At least 2 Physicians*:	Kenneth Mayer, Joel Gallant
DAIDS Medical Officers:	Vanessa Elharrar
Protocol Statistician:	Ying Q. Chen
SDMC Clinical Safety Specialist:	Donna Robinett

*Note: The physicians on the HPTN 052 PSRT must be experienced in the care and treatment of HIV/AIDS patients, including ART management.

The physicians will serve as the alternative PSRT Chairs.

Ideally all of the above-listed PSRT members will take part in routine PSRT conference calls; however, a quorum of at least four active members must take part in all calls. The quorum must consist of:

- 1) PSRT Chair or one alternate Chair;
- 2) At least one DAIDS Medical Officer;
- 3) Protocol Statisticians or a temporary replacement; **and**
- 4) One additional physician with experience in HIV/AIDS treatment and ART management

If a quorum is not present, the call may be deferred until the next scheduled call time unless a quorum member requests a more immediate call.

For purposes of summarizing the PSRT conference calls, one or more of the HPTN CORE (FHI) Clinical Research Managers will receive the reports and attend the calls. When appropriate, there may be other observers to the PSRT calls, including:

- CORE Associate Directors (ADs)
- SDMC Project Managers
- SDMC Statistical Research Associates
- DAIDS PAB Protocol Pharmacist
- Pharmaceutical Co-Sponsors
- HPTN Network Lab

9.2.11.3 Routine Safety Data Summary Reports: Content, Format, and Frequency

The PSRT has the authority to determine or modify the content and format of the safety data reports, which may evolve as the study progresses. The SDMC will generate and send standard safety data reports to the PSRT Chair for review on a weekly basis unless otherwise specified by the Chair. The SDMC will also generate and send reports to the active members of the PSRT via e-mail 7 days prior to each monthly PSRT conference call. Tabulations will be generated for all study participants combined (*i.e.*, across both treatment groups) for individual sites and overall. The following data will be included in the standard safety data reports:

- Demographics
- Prior ART Exposure
- MedDRA Coded Adverse Event Frequency by Body System
- MedDRA Coded Adverse Event Frequency by MedDRA Term and Severity Grade
- MedDRA Coded Adverse Event Frequency by MedDRA Term and Relationship to Treatment
- Graded Lab Abnormalities by Visit and Overall
- Pregnancy Outcomes
- ART Use
- Study termination Associated with AE
- Reported Adverse Events not Coded in MedDRA

Individual participant profile reports will be supplied on an ad hoc basis in response to specific queries resulting from PSRT review.

Each distribution of the safety data reports will consist of one set of reports containing cumulative data and one set listing only new events reported since the last distribution. New events are defined as any Adverse Event changes in MedDRA coded diagnosis or in severity.

9.2.11.4 PSRT Communications

An email alias (052PSRT@HPTN.org) will be used to facilitate communication with the PSRT. All safety data summary reports from the SDMC will be distributed via this alias.

9.2.12 Documenting and Grading AEs

For the purposes of HPTN 052, an adverse event (AE) is defined as any untoward medical occurrence in an Index Case participant **after the participant has been randomized to either arm of the study**. As such, an AE can be an unfavorable or unintended sign (including abnormal laboratory findings), symptom, or disease that may or may not be considered related to the study drug. Conditions and illnesses identified in Index Case participants prior to randomization will be reported as pre-existing conditions and will not be considered AEs.

Study site investigators are responsible for documenting all AEs in the study source documentation, and for reporting via DataFax all Grade 3 and higher AEs occurring in Index Case participants, **regardless of whether or not the participant has been exposed to study drug**, in the Index Adverse Event Log (DataFax CRF). Although participants not on ART will not be exposed to study drug, and therefore there is no possibility of relatedness to the study drug, reporting events in both arms will allow for comparison of AEs between the two groups. All AEs will be graded according to the current version of the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events* (the table can be downloaded at http://rcc.tech-res-intl.com/tox_tables.htm). AEs that are less than Grade 3 will be recorded and graded in the study source documentation, but will not be reported on the Index Adverse Event Log. Laboratory results that are outside of the normal range, but are not abnormal enough to reach a Grade 1, can be identified as “NCS” (not clinically significant) in the source documentation if so determined by a study clinician.

HIV/AIDS related conditions, WHO Stage 2 and 3 events, and other targeted medical conditions found in Appendix IV of the HPTN 052 protocol (LoA#1 to V. 3.0 of the protocol) will be recorded on the When-to-Start DataFax form for entry into the study database. These events may also be included in the Index Adverse Event Log if they are Grade 3 or higher.

Clinical information about Partners should be recorded in clinic notes; however, AEs will not be reported for Partners.

All information obtained while conducting directed follow-up physical examinations, follow-up review of symptoms, and laboratory tests on Index Cases should be recorded in the source documentation according to site SOPs. This information should be reviewed after each participant visit to determine if an AE or an HIV/AIDS-related event, WHO Stage 2 and 3 events, or other targeted medical condition has occurred and should be reported in the appropriate CRF. Whenever possible, the final diagnosis, rather than the individual signs and symptoms, should be documented in the source documentation and the Index Adverse Event Log; however, if a diagnosis is not possible, each individual sign and symptom should be reported.

All signs, symptoms, and diagnoses reported as AEs must be assessed as to their

relatedness to study drug. For the purposes of HPTN 052, this will include all HIV ART whether it is provided by the study or the site. Relatedness assessments should be made according to the definitions contained in the *Manual of Expedited Reporting of Adverse Events to DAIDS* (the manual can be downloaded at <http://rcc.tech-res-intl.com/eae.htm>). The relatedness categories include definitely related, probably related, possibly related, probably not related, and not related. Note that the *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-CL-04.00)* requires that a definitive alternate etiology be documented for all signs, symptoms, and diagnoses reported as AEs and assessed as “not related.”

Any questions regarding the grading or management of AEs should be directed to the HPTN 052 clinical management committee via email (052CMC@hptn.org).

Table 9-3 summarizes how AEs and HIV/AIDS-related events will be captured for HPTN 052.

Table 9-3: Capturing AEs and HIV/AIDS-related events for HPTN 052

Event	Index Case	Partner
All signs, symptoms, and diagnoses	Clinic notes and lab results (source documentation only)	Clinic notes and lab results (source documentation only)
AEs < Grade 3	Clinic notes and lab results (source documentation only)	Clinic notes and lab results (source documentation only)
AEs ≥ Grade 3	Index Adverse Event Log (DataFax CRF)	Clinic notes and lab results (source documentation only)
HIV/AIDS-Related events, WHO Stage 2 and 3 events, targeted medical conditions	WTS (DataFax CRF)	Clinic notes and lab results (source documentation only)

WTS, When-to-Start

Each site must develop a system for collecting signs, symptoms, and diagnoses and ensuring that these events are captured appropriately for HPTN 052. Table 9-4 shows one way this type of data may be collected in the source documentation. In this example, the Signs, Symptoms, and Diagnoses Log would be continually assessed to determine whether an AE or an HIV/AIDS-related event, WHO Stage 2 and 3 events, or other targeted medical condition should be recorded on a DataFax CRF. It is not mandatory for sites to use this log as part of their source documentation.

Table 9-4: Signs, Symptoms, and Diagnoses Log with Example Data

No.	Sign, Symptom, or Diagnosis	Start Date	End Date	Grade	Relationship to study drug	HIV/AIDS-Associated Diagnosis?	If Diagnosis: Confirmed, Probably, Presumptive, Clinical Diagnosis Only	If Sign or Symptom Becomes Part of a Diagnosis, Indicate Diagnosis Number, Initial and Date	Staff Initials and Date
1	Fever	01 Jan 03	15 Jan 03	2	Possibly related	No	N/A	3, ABC 05 Jan 03	ABC 02 Jan 03 ABC 15 Jan 03
2	Skin Rash	01 Jan 03	15 Jan 03	2	Possibly related	No	N/A	3, ABC 05 Jan 03	ABC 02 Jan 03 ABC 15 Jan 03
3	Stevens Johnson Syndrome	05 Jan 03	15 Jan 03	3	Definitely related	No	Clinical Diagnosis Only	N/A	ABC 05 Jan 03 ABC 15 Jan 03 ABC 15 Jan 03
4	Cough	15 Jan 03	20 Jan 03	1	Not related	No	N/A		ABC 15 Jan 03
5	Diarrhea	12 Feb 03	20 Feb 03	3	Possibly related	No	N/A	6, ABC 16 Feb 03	ABC 15 Feb 03 ABC 17 Mar 03
6	Microsporidiosis	12 Feb 03	20 Feb 03	3	Not related	No	Confirmed	N/A	ABC 16 Feb 03 ABC 17 Mar 03 ABC 17 Mar 03
7	Hemoglobin	17 Mar 03		1	Possibly related	No	N/A		
8	Herpes Zoster (shingles)	15 Mar 03		3	Not related	Yes	Confirmed	N/A	ABC 17 Mar 03

Events 3 and 6 would be recorded on the AE Log; event 8 would be recorded on the AIDS-Associated Event Log.

Instructions for completing Sign, Symptom, and Diagnosis Log: No.: Give each sign, symptom, and diagnosis a sequential number. **Sign, Symptom, or Diagnosis:** If possible, record a diagnosis; however, if the diagnosis is unknown, record individual signs and symptoms. **Start Date:** Date the event started. **End Date:** Date the event ended. If the event is ongoing, leave blank. At the end of the study, enter “ongoing” for all events that have not ended. **Grade:** Use the DAIDS Toxicity Table to grade the severity of each sign, symptom, and diagnosis. All events of grade 3 and higher should be entered into the AE Log CRF. **Relationship to Study Drug:** Record one of the following: definitely related, probably related, possibly related, probably not related, not related. **AIDS-Associated Diagnosis:** Use Appendix IV of the HPTN 052 protocol (per LoA #1 to V. 3.0) to indicate (yes/no) if an event is an HIV/AIDS—associated diagnosis. **If Diagnosis: Confirmed, Probably, Presumptive:** Use ACTG Appendix 60 (International Diagnoses Appendix) to indicate whether a diagnosis is confirmed, probably, or presumptive. If the event is a sign or symptom, enter N/A (not applicable). **If Sign or Symptom Becomes Part of a Diagnosis, Indicate Diagnosis Number:** If a sign or symptom is identified as part of a diagnosis after it is recorded in this log, identify the corresponding diagnosis by number and initial and date entry. If the event is a sign or symptom, but it is not known whether it is part of a diagnosis, leave blank. If the event is a diagnosis, enter N/A (not applicable). **Staff Initials and Date:** Initial and date the original entry in the top row, initial and date the end date entry in the bottom row.

9.2.13 Expedited Reporting of Adverse Experience (EAEs)

Study site investigators are responsible for using the *Manual for Expedited Reporting of Adverse Events to DAIDS* (the manual can be downloaded at <http://rcc.tech-res-intl.com/eae.htm>) to report expedited AEs (EAEs) occurring in Index Case participants **who have been exposed to study drug**. In addition, investigators must report events that meet the criteria for expedited reporting due to study participation or study-related procedures (for example domestic violence or severe infections due to blood draws). The standard level of reporting as defined in this manual is required for HPTN 052. In addition, the standard level of EAE reporting is required for infants born to mothers on study drugs until they are 18 months of age. For the purposes of expedited reporting of adverse events, the study drugs are: atazanavir (ATV), Combivir (3TC/ZDV), didanosine (ddI-EC), efavirenz (EFV), lamivudine (3TC), nevirapine (NVP), stavudine (d4T), tenofovir (TDF), Kaletra[®]/Aluvia[®] [lopinavir(LPV)/ritonavir (r)], and Truvada[®] [emtricitabine (FTC)/tenofovir (TDF)].

Study site investigators are responsible for reporting information on EAEs to the responsible Institutional Review Boards/Ethics Committees in the US and the host countries in accordance with applicable regulations and individual IRB/EC requirements.

For the purposes of this study, an adverse event that meets the EAE reporting criteria (Standard Level) is defined as an AE following any exposure to study agent that:

- Results in death **regardless** of relationship to study agent.
- Are congenital anomalies, birth defects, or fetal losses **regardless** of grade or relationship to study agent.
- Results in persistent or significant disabilities or incapacities **regardless** of relationship to study agent.
- Are a **suspected adverse drug reaction (SADR)** (*i.e.*, definitely, probably, possibly, and probably not related to a study agent) that requires or prolongs existing hospitalization, or requires intervention to prevent significant/permanent disability or death.
- Are life-threatening (including all Grade 4 AEs) **suspected adverse drug reactions (SADRs)** (*i.e.*, definitely, probably, possible, and probably not related to a study agent.)

The timeframe for expedited reporting of individual AEs begins when the site recognizes that an event fulfils the criteria outlined in the *Manual of Expedited Reporting of Adverse Events to DAIDS*. Sites must submit EAEs to the DAIDS Safety Office as soon as possible, **but no later than 3 business days**, after the site's recognition that the event fulfils the criteria for expedited reporting.

As noted above, all congenital anomalies, birth defects, and fetal losses

(spontaneous abortions) must be reported as EAEs regardless of grade and relationship to the study drug. Like all other EAEs, these events must be graded for severity; however, the generic scale (1 [mild], 2 [moderate], 3 [severe], 4 [life-threatening]) should be used as there is no specific listing for these events in the *Table for Grading the Severity of Adult and Pediatric Adverse Events* (the table can be downloaded at http://rcc.tech-res-intl.com/tox_tables.htm). For example, a spontaneous abortion occurring during the first 4-8 weeks of pregnancy that was associated with no significant pain or heavy bleeding would be categorized as a Grade 1; whereas, a spontaneous abortion that resulted in an in-patient procedure with complications would be classified as a Grade 3. In both of these examples, an EAE would be required to report, regardless of grade.

When reporting EAEs for infants born to mothers on study drugs, the primary AE should be preceded by the word “BABY” and the mother’s PTID should be used in the EAE form. For example, when reporting a Grade 4 pneumonia in a hospitalized infant, the primary AE on the DAIDS EAE reporting form should read: “BABY-pneumonia” and the mother’s PTID should be used. This procedure is necessary to distinguish EAEs that occur in study participants from their infants, as infants are not assigned a unique PTID for HPTN 052.

Hospitalizations should only be reported as an EAE if the reason for hospitalization is an AE. For example, hospitalization for normal childbirth is not considered an EAE, as childbirth is not an AE.

The requirements and definitions for expedited reporting of adverse events (AEs) to the DAIDS RCC Safety Office are defined in “The Manual for Expedited Reporting of Adverse Events to DAIDS” (DAIDS EAE Manual) dated May 6, 2004. The DAIDS EAE Manual is available on the RCC website: <http://rcc.tech-res-intl.com>.

Sites using the DAERS internet-based reporting system for submission of EAEs to DAIDS will follow the DAERS processes as outlined in the DAERS training information. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within the DAERS application itself.

If the site cannot use DAERS to report an AE on an expedited basis, the AE must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) available on the RCC website: <http://rcc.tech-res-intl.com> and submitted as specified by the DAIDS EAE Manual. For questions about EAE reporting, please continue to contact the RCC. The requirements and definitions for expedited reporting of adverse events (AEs) to the DAIDS RCC Safety Office are defined in “The Manual for Expedited Reporting of Adverse Events to DAIDS” (DAIDS EAE Manual) dated May 6, 2004. The DAIDS EAE Manual is available on the RCC website: <http://rcc.tech-res-intl.com>.

Table 9-5 provides a reference for deciding if an event needs to be reported as an AE or an EAE for study participants.

Table 9-5: Reference Guide for Reporting AEs, HIV/AIDS-related Conditions, WHO Stage 2 and 3 Events, Other Targeted Medical Conditions, and EAEs

Type of Adverse Event	All Index Cases (on AND not on ART)	Partner	All Index Cases (on AND not on ART)	Partner	Index Case on ART	Index Case NOT on ART	Partner
	Report on SCHARP AE log		Report on WTS CRF		Report as EAE		
Results in death	Yes	No	Possibly*	No	Yes, regardless of relationship to ART	No	No
Congenital anomaly, birth defect, or fetal loss	No, report on pregnancy outcome form	No	No	No	Yes, regardless of grade and relationship to ART	No	No
Results in persistent or significant disabilities or incapacities	Yes	No	Possibly*	No	Yes, regardless of relationship to ART	No	No
Requires/prolongs hospitalization or requires intervention to prevent significant/permanent disability or death	Yes	No	Possibly*	No	Report as EAE if relationship to ART is definitely, probably, possibly, or probably not related	No	No
Is life-threatening (includes all Grade 4 AEs)	Yes	No	Possibly*	No	Report as EAE if relationship to ART is definitely, probably, possibly, or probably not related	No	No
Other Grade 3 AEs	Yes	No	Possibly*	No	No	No	No
Is considered a <u>serious AE</u> that is <u>not related to study</u> <u>product</u> , but could be associated with study participation or procedures	Yes	No	No	No	Yes	Yes	Yes
Other Grade 1 and 2 AEs	No	No	Possibly*	No	No	No	No
HIV/AIDS-related Illnesses†	If Grade 3 or higher	No	Yes	No	Possibly**	No	No
WHO Stage 2 and 3 Clinical Events†	If Grade 3 or higher	No	Yes	No	Possibly**	No	No
Other Targeted Medical Conditions†	If Grade 3 or higher	No	Yes	No	Possibly**	No	No

WTS: When-To-Start

† As listed in Appendix IV of HPTN 052, V3.0 (per LoA #1)

* If listed in Appendix IV of HPTN 052, V3.0 (per LoA #1)

** If it meets the definition of an EAE.

9.2.14 HPTN 052 Product Safety Information

Once a site has completed protocol registration, it will begin to receive product safety information on the study drugs. This information may be:

- Revised investigator brochures
- Revised package inserts
- IND safety reports
- Safety memos, reports, or updates
- Reports of DSMB review
- Safety Notices/Alerts

This information will be forwarded to the sites by the HPTN CORE via email and each site should maintain copies of each communication in their regulatory files. This information originates from the Regulatory Compliance Center (RCC). Each email will indicate how the information is to be handled. In many cases, this information must be submitted to all responsible IRBs/ECs. Product safety information does not require IRB/EC approval; however, sites should maintain copies of the IRB/EC submission cover letters indicating the date of submission and identifying the submitted documents in their regulatory files. The Investigator of Record and Study Coordinator are responsible for reviewing this information, disseminating the information to their staff, and ensuring that it is submitted to the U.S. and local IRBs overseeing the study.

9.3 Counseling Procedures

9.3.1 Pre-and Post-HIV Test Counseling

HIV testing is required during screening and on a quarterly basis for the HIV-uninfected Partner throughout the duration of HPTN 052. Each site is required to develop a local SOP for pre- and post-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 him/her to decide for himself/herself whether to be tested (informed decision with informed consent).
- The HIV testing procedure should be organized to maximize confidentiality.
- HIV antibody 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.

Post-test counseling should be conducted when the test results are available, which may be at the day of testing or the next scheduled visit. If it is convenient for the participant, or it is part of a site's standard of care, interim visits may be scheduled to give HIV test results and conduct post-test counseling.

The site-specific SOPs should be consistent with the guidelines set forth by the CDC in 2001 entitled, "Revised Guidelines for HIV Counseling, Testing, and Referral." This document can be downloaded at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5019a1.htm>.

Another resource that may be useful for HIV pre- and post-test counseling is entitled, "HIV Voluntary Counseling and Testing (VCT): A Reference Guide for Counselors and Trainers," which was developed by the Institute for HIV/AIDS at Family Health International in May 2003. A copy of this document can be requested from the HPTN CORE.

9.3.2 Adherence Counseling

All couples in which the HIV-infected individual is on ART will undergo adherence counseling. If at all possible, both members of the couple should participate in this counseling.

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

- Emphasis on building good communication and rapport between the study participant and the counselor and physician.
- Definition of and education about ART adherence, including barriers to adherence.
- Education about each component of the ART prescribed to the participant, including the dose, frequency, and expected side effects.
- Pill dispensing and accounting.
- Creation or review of daily medication schedule, including reminder strategies and plans to overcome anticipated obstacles.
- Discussion of social support and privacy.

- Strategies to handle non-adherence.
- Discussion about side effects, expectations, and contacting providers.
- Ways in which the non-HIV-infected individual can help his or her Partner be adherent.

Checklists for adherence counseling will be provided by the HPTN CORE and available on the HPTN 052 website:

http://www.hptn.org/research_studies/HPTN052StudyDocuments.asp

9.3.3 Couples Counseling

Participation in couples counseling is required for HPTN 052. This counseling is not intended to be a substitute for marriage counseling or other forms of psychotherapy; rather it should focus on issues surrounding the HIV-serodiscordant status of the couple, particularly safe sex practices.

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

- Assessing the couple's knowledge of HIV/AIDS and providing appropriate information.
- On-going education about the transmission and prevention of HIV infection.
- Demonstrate the proper use of condoms and provide free condoms. A condom demonstration must be conducted at the first couples counseling session and at least annually thereafter; however, staff are encouraged to provide this demonstration as often as they deem necessary for a given couple.
- Emphasis on building good communication between the Partners.
- Discussion of family and community pressures and conflicts.
- A referral strategy for additional counseling, drug or alcohol abuse, and domestic violence.

The U.S. CDC has develop materials for couples HIV counseling and testing interventions, along with a training curriculum. These materials may be found here:

<http://www.cdc.gov/nchstp/od/gap/CHCTintervention/>

Checklists for couples counseling will be provided by the HPTN CORE and available on the HPTN 052 website:

http://www.hptn.org/research_studies/HPTN052StudyDocuments.asp