

## Section 5. Participant Follow-up

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This section describes the timing and scheduling of participant follow-up visits and visit procedures. These procedures are also described in detail in the protocol and in Section 6 Visit Checklists in this manual. Section 7 covers participant retention during follow-up, while Section 8 details study drug dosing requirements. Clinical and laboratory procedures, including pharmacokinetics (pk) specimen collection, can be found in Sections 9 and 10. Adverse event (AE) reporting requirements are described in Section 11.

### 5.1 Follow-up Period

As described in Section 4, mothers and their infants will be screened and enrolled over approximately 6-9 months for Cohorts 1 - 3, with enrollment in Cohort 3 beginning after all mothers and infants in Cohorts 1 and 2 have been followed for a minimum of 6 weeks. Cohort 4 will open after Cohorts 1, 2 and 3 have completed follow-up - participants are expected to be screened and enrolled over approximately 6 months for Cohort 4. Each mother/infant pair will be followed through 12 months postpartum.

### 5.2 Follow-up Visits

There are two types of follow-up visits, scheduled and interim:

- **Scheduled visits** are conducted during follow-up as stated in the study protocol.

Scheduled maternal follow-up visits for all 4 cohorts occur at 24-48 hours, 5 to 7 days, 6 and 12 weeks, and 6 and 12 months. In addition, pk sampling will be performed on mothers enrolled in Cohorts 1 and 3 during the 36 to 48 hour period after receiving tenofovir disoproxil fumarate (TDF). The delivery sample will be the only pk sample collected for mothers in Cohort 4. (The collection of these pk specimens may not fall on a scheduled visit. See Section 10.1.6 for the complete pk schedule.)

Scheduled infant follow-up visits for Cohorts 2, 3 and 4 occur within 24 hours of birth, 5 to 7 days, 6 and 12 weeks, 6, 9 and 12 months. In addition, pk sampling will be performed on infants during a 48 hour period after birth in Cohort 1, before and after receiving each TDF dose in Cohorts 2 and 3, and during a 24 hour period after the birth, 4<sup>th</sup> and 7<sup>th</sup> dose in Cohort 4 with (the 24 hour sample for the birth and 4<sup>th</sup> dose collected just before the next dose of study drug is given). (The collection of these pk specimens may not fall on a scheduled visit. See Section 10.2 for the complete pk sample schedule.) All scheduled follow-up visits are pre-assigned a visit code as described in Section 12.6 and have a specific target date for completion relative to the date of birth (Day 0) with an allowable visit window.

A scheduled visit is considered a 'missed visit' if it is not completed within the defined visit window. Section 5.5 below and Section 12.7 of this SSP Manual describe follow-up visit scheduling procedures.

- **Interim visits** are those that take place between scheduled visits. Interim visits may take place for a number of reasons, e.g., a participant may be sick or additional testing may be required. A DataFax form is required for all visits at which data to be entered into the study database is collected; see Section 12.6.1 for instructions on assigning interim visit codes. All visits for both mothers and infants including the purpose of the visit and the results of all evaluations including interim laboratory tests must be recorded in study source documents and on the relevant DataFax Case Report Forms (CRFs), as described in Section 12. This includes an Interim Visit CRF and, if relevant, an AE Log, Laboratory Results CRF, Concomitant Medications Log and/or Antiretroviral Medications Log.

### 5.2.1 Follow-up Visit Locations/Off-site Visits

Study follow-up visits must take place at the study clinic. No study-specific assessments or evaluations can be conducted off-site, and no study drug can be dispensed off-site.

Home/off-site visits will be conducted throughout the study to remind mothers of scheduled visits, to follow up on missed visits, and to request interim visits for additional lab testing or other assessments, as needed. Home/off-site visits are not considered study follow-up visits and should not involve any study assessments, or collection of any study data, including information on AEs. Instead, mothers should be instructed to report any illnesses or other problems to the study staff at the clinic. If necessary and locally acceptable, transportation to the clinic may be provided to ensure a visit is completed. Information reported by mothers during scheduled or interim visits is considered source data, while information learned during a home/off-site visit is not. Information reported by mothers during scheduled clinic visits or interim visits is considered the source of study data rather than information reported during home/off-site visits. If a home visitor/outreach worker learns of a participant's death or condition that would preclude return to the study clinic, he/she should report this right away to the Investigator and his/her designee(s) at that site (e.g. Study Coordinator) for appropriate follow-up and documentation.

Each site is responsible for developing a system for organizing and overseeing of home/off-site visits. For continuity, it is recommended that each mother/infant pair be assigned to a single home visitor to follow them throughout the study. Home visitors should be familiar with the locator information provided by the study participant and should at all times respect the participant's wishes about when, where and how she may be contacted. Client confidentiality must be maintained during home visits.

As noted in Section 3.2.3, each site's SOP for data management must specify procedures for handling participant study records for off-site visits.

## 5.3 Scheduled Follow-up Procedures

The scheduled follow-up procedures for mothers and infants are listed below:

### 5.3.1 Mothers

The following procedures must be performed at all scheduled maternal follow-up visits:

- Interim Medical History
- Symptom-directed physical
- Blood Specimen Collection (see Section 10)
- Breast Milk Collection (only for mothers who are breastfeeding up to 12 weeks.)

See section 5.4 for exceptions to these procedures.

### 5.3.2 Infants

Following are the infant follow-up visit procedures.

- Interim Medical History
- Full Physical Exam
- Blood Collection (except 9 month visit)
- Dried Blood Spot Storage (except 9 months)
- Thoracic spine and left wrist x-ray (Day 3 and Week 12 only), Cohorts 1, 2 and 3 only.

See section 5.4 for exceptions to these procedures.

## **5.4 Special Circumstances Affecting Follow-up Assessments**

Circumstances may arise that affect the procedures to be conducted at scheduled follow-up visits. These include: failure to receive TDF, death of the infant or mother, and early withdrawal/termination of both the mother and infant from study participation. *Note: All enrolled mothers and infants exposed to study drug will remain in the study and complete all follow-up visits as scheduled, unless informed consent is withdrawn or invalidated or the mother is not dosed (Cohorts 1 and 3) or infant is not dosed (Cohort 2 only).*

### **5.4.1 Mother and Infant Not Exposed to Study Drug**

- If a mother enrolled in Cohort 1, 3 or 4 does not receive the study drug for any reason, then both the mother and infant should be terminated and for infants enrolled in Cohorts 3 and 4, the infant should not be dosed. not be given. The reason the mother was not dosed should be documented in study source documents. If Cohort 2 is open for enrollment, the pair can be re-assigned to Cohort 2.
- If a mother enrolled in Cohort 2 delivers a still birth, then the mother should be terminated and the reason the mother was terminated should be documented in study source documents.

In these two circumstances above, no infant CRFs are required. The following maternal CRFs are required:

- ♦ Mother Demographics
  - ♦ Mother Screening Lab Results
  - ♦ Mother Enrollment and Delivery
  - ♦ Mother Enrollment labs (if done)
  - ♦ Mother Termination
- If an infant enrolled in Cohort 2 is not dosed for any reason (i.e. the dose is missed or the infant does not meet the initial dosing criteria as specified in Section 3.4 of the study protocol) then the mother and infant should be terminated. The reason the infant was not dosed should be documented in study source documents. The following CRFs are required:
    - ♦ Mother Demographics
    - ♦ Mother Screening Lab Results
    - ♦ Mother Enrollment and Delivery
    - ♦ Mother Enrollment labs (if done)
    - ♦ Mother Termination
    - ♦ Infant Birth
    - ♦ Infant Pre-existing Conditions
    - ♦ Infant Enrollment Lab Results (if done)
    - ♦ Infant Concomitant Medications

- ◆ Infant Termination

#### **5.4.2 Mother and/or Infant Exposed to Study Drug But Not Evaluable**

- Infants in Cohorts 2, 3 and 4 who have study drug discontinued will remain in follow-up and undergo all procedures except pk specimen collection for the doses missed. (See section 10.1.6 of this manual for pk specimen collection procedures).
- If an infant enrolled in Cohorts 3 and 4 does not meet the initial dosing criteria as specified in Section 3.4 of the study protocol the mother and infant pair will remain in follow-up and undergo all procedures except collection of pk specimens. (See Section 10.1.6 of this manual for pk specimen collection procedures).
- If a mother enrolled in Cohort 1, 3, or 4 does not deliver within 24 hours of dosing or vomits, no pk specimens should be collected from the mother or infant. The infants born to mothers enrolled in Cohorts 3 and 4 should not be dosed. The mother and infants will remain in follow-up and undergo all study procedures except pk sampling.
- If an infant in Cohort 4 misses or vomits his/her birth, 4th or 7th dose of TDF the PK specimens associated with (following) that dose should not be obtained. Subsequent dosing and PK sampling will not be done. The mother and infants will remain in follow-up and undergo all study procedures except dosing and pk sampling.
- If an infant in Cohort 4 vomits the 2nd, 3rd, 5th or 6th dose of TDF and the infant is not re-dosed then subsequent dosing and PK sampling will not be done. The mother and infants will remain in follow-up and undergo all study procedures except dosing and pk sampling.
- If an infant pk specimen (Cohorts 1, 2, 3 and 4) is missed for any reason no further dosing or pk sampling will be done on the mother and infant. The mother and infants will remain in follow-up and undergo all study procedures except dosing and pk sampling

#### **5.4.3 Infant Death**

If an infant enrolled in Cohort 2 dies, the mother will be terminated from the study. If an infant enrolled in Cohort 1, 3 or 4 dies, the mother will remain in follow-up.

#### **5.4.4 Maternal Death**

If a mother enrolled in the study dies, the infant will remain in follow-up.

- All study-specific assessments and visits should be discontinued until or unless written informed consent is obtained from the father or legal guardian for the infant's continuation in the study. The clinic should continue to provide care per standard procedures.
- If written informed consent is obtained from the father or legal guardian, the infant should resume all study visits and evaluations as scheduled.

#### **5.4.5 Early Termination of Mother and/or Infant for Reason other than Death**

Mothers may choose to terminate their own and/or their infant's participation in the study at any time. The investigator may withdraw participants from the study to protect their safety and/or if they are

unwilling or unable to comply with required study procedures after consultation with the Protocol Chair, NIH Medical Officer, the Protocol Statistician, the CORE Protocol Specialist and SDMC Project Manager. The study also may be stopped early by the sponsor or local authorities.

Should a mother or infant's participation in the study be terminated for any reason before the 12-month study visit the mother and infant will be asked to have several final clinical and laboratory evaluations performed prior to termination, if possible.

Maternal evaluations will include:

- Interim medical history
- Symptom directed physical exam
- Hematology (thru 6 week visit)
- Chemistries (thru 6 week visit)
- Plasma storage for HIV RNA or DNA PCR testing and TDF resistance
- Breast milk storage (thru 12 week visit if breastfeeding)

Infants whose mothers wish to terminate their participation will have the following clinical and laboratory evaluations performed prior to termination, if possible:

- Medical history
- Physical exam
- Hematology (thru 12 week visit)
- Chemistries (thru 12 week visit)
- Roche Amplicor HIV-1 DNA PCR
- Plasma for storage (for TDF resistance, HIV-1 RNA or DNA PCR, and TDF concentration)

*Note: These assessments should be performed only if the participant is available and willing; it is imperative that the mother's wishes be respected with regard to elective termination from the study. The mother's agreement or lack thereof for these final assessments should be documented in the participant's study record. If the infant or mother is not available for these assessments, this should be also documented.*

## **5.5 Follow-up Visit Scheduling**

Detailed instructions regarding the timing of scheduled visits for mothers and infants are included in Section 12.7.

### **5.5.1 Target Visit Dates**

Each protocol-specified visit should be completed on or as close as possible to the target date. Sites are responsible for establishing follow-up procedures to ensure maximum adherence to the visit schedule. If a participant visit is outside the allowable visit window, the next visit should be completed on or about the date originally scheduled – i.e., not adjusted relative to the actual completion date of the previous visit.

### **5.5.2 Allowable Visit Windows**

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, visits may be completed within an allowable window around the target date, though it is preferable to complete visits as close to the scheduled date as possible. The target visit day and corresponding windows are described in Section 12.7 of this SSP Manual. The allowable windows for pk sampling are described in Section 10.2.

Although the visit windows allow considerable flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits at set intervals. Extreme deviation from the protocol specified time points should be avoided. Adherence to the target visit schedule will be closely monitored by the study team and the HPTN Study Monitoring Committee.

### 5.5.3 Missed Visits

For participants who do not complete scheduled visits within the allowable window, the visit will be considered “missed,” and a Missed Visit CRF will be completed. Section 12.7.1 includes detailed information on the procedures to be followed in the event of a missed visit.

If a participant misses a visit but presents to the clinic soon after the visit window has closed only to report or seek care for an illness/AE or to obtain additional study product, an interim visit would be conducted rather than the next scheduled visit. The mother would be reminded to return for the next scheduled visit closer to the target visit date, unless there is a reason to believe that it is unlikely that the participant will return for that clinic visit (e.g., the participant reports that she will out of the area for a while). In this case, it is preferable to complete the next scheduled visit well before the target date, but within the visit window, than for the participant to potentially miss the scheduled visit entirely.

If a mother/infant pair misses three consecutive follow-up visits despite multiple documented unsuccessful attempts to contact them or if study staff definitely learns of another reason that their continued participation in the study is not possible or is extremely unlikely (such as permanent relocation to another area), the participants may be terminated. Staff should complete the Mother’s and Infant’s Termination, End of Study Inventory, Antiretroviral Medication Log, Concomitant Medications Log DataFax forms and submit these to the SDMC. If the participants later return to the study clinic and wish to continue their participation in the study, they can be “reactivated” and their participation fully resumed. See Section 12.8 for more detailed information about termination and reactivation of participants.

Note that the goal is to retain ALL enrolled mothers and infants throughout the entire 12-month follow period.

## 5.6 Infant HIV Testing

If an infant has an initial positive HIV DNA or RNA PCR result suggesting HIV infection, the mother should be contacted and asked to bring the infant to the clinic for a confirmatory test as soon as possible according to standard local procedures and no later than the next scheduled study visit.

*Note: Accurate HIV testing and result recording are essential to the success of this study. Prior experience has indicated a critical need to implement strict quality control/quality assurance (QC/QA) procedures to ensure the quality of HIV testing and result recording. Each site must establish clinic and laboratory SOPs to ensure the quality of specimen collection and labeling as well as HIV testing procedures. For result reporting, site SOPs must designate adequate internal review procedures to ensure that all test results are recorded accurately on local testing logs, other source documents, and case report forms and that appropriate study staff are promptly notified of a positive test result. All sites are strongly encouraged to keep original test result runs or strips for daily review and verification of result recording and transcription before discarding. Contact the HPTN Network Lab for further guidance on site SOPs for HIV testing and result recording.*

### 5.6.1 Infant HIV Testing Procedures

HIV DNA or RNA PCR tests will be used to test infants for HIV infection. If the initial PCR is negative, the participant will be considered uninfected at that time point. If the initial test is positive or indeterminate, a second specimen will be collected on a different day (as soon as possible but no later than the next scheduled visit) to be tested by HIV DNA or RNA PCR for confirmation. If the initial sample and the second sample are positive the infant will be considered HIV infected. If the initial sample is indeterminate and the second sample is negative, indeterminate, or positive, additional testing is required on a different specimen at or before the next scheduled visit. An infant will be considered HIV-infected only if two separate blood specimens drawn on different days are each positive by HIV DNA or RNA PCR.

## **5.7 Participant Transfers**

Transfer of participants in HPTN 057 from one research center to another (e.g., from Belo Horizonte to Porte Alegre) is expected to be very rare. However, if a participant notifies the original enrollment site that she is moving to a location where the study is being conducted, she should be encouraged to continue in the study. Study staff at both sites will need to complete a formal participant transfer process. The study coordinator or investigator at each site must contact the CORE Protocol Specialists, the SDMC Project Manager and the DAIDS Protocol Pharmacist at Pharmaceutical Affairs Branch (PAB) for complete transfer instructions *before* any study related activities are conducted at the receiving site.