

Section 4. Participant Accrual

This section provides an overview of requirements and procedures for the screening and enrollment of mothers and infants in the study. The study screening and enrollment procedures are described in the study protocol (Section 3) and detailed in the visit checklists in Section 6 of this manual. Additional instructions for clinical and laboratory procedures can be found in Sections 9 and 10 of this manual, respectively.

4.1 Recruitment and Target Enrollment

A total of 110 fully-evaluable mother/infant pairs will be enrolled in approximately equal numbers across the two sites – with about half of each cohort in Brazil and half in Malawi. A mother/infant pair is established as fully-evaluable when a complete set of pk samples has been obtained as specified in the protocol (Section 5.6) and in Section 10 of this manual. See tables below for a breakdown of the enrollment estimates by site, mode of delivery and cohort.

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

The enrollment numbers for each cohort are as follows:

Cohort 1: Mothers only receive TDF

	Vaginal Deliveries	C-section Deliveries	Approximate # of evaluable mother/infant pairs at each site	TOTAL # of evaluable mother/infant pairs
Blantyre	~ 8 to 15	~ 0 to 7	~ 15	30
Brazil Sites	~ 8 to 15	~ 0 to 7	~ 15	

Cohort 2: Infants only receive TDF *Note: mode of delivery is not an issue.*

	Approximate # of evaluable mother/infant pairs at each site (vaginal and c-section deliveries)	TOTAL # of evaluable mother/infant pairs
Blantyre	~ 10	20
Brazil Sites	~ 10	

Cohort 3: Mothers and infants receive TDF

	Vaginal Deliveries	C-section Deliveries	Approximate # of evaluable mother/infant pairs at each site	TOTAL # of evaluable mother/infant pairs
Blantyre	~ 8 to 15	~ 0 to 7	~ 15	30
Brazil Sites	~ 8 to 15	~ 0 to 7	~ 15	

Cohort 4: Mothers and infants receive TDF

Note: There is NO restriction on the number of Caesarean section deliveries for Cohort 4

	Approximate # of evaluable mother/infant pairs enrolled in each country	TOTAL # of evaluable mother/infant pairs
Blantyre	~ 15	30
Brazil Sites	~ 15	

Site staff is responsible for establishing an accrual plan for this study, and for updating the plan and recruitment strategies if needed to meet the accrual goals. The recruitment plan minimally should contain the following elements:

- Site-specific weekly accrual goals
- Recruitment methods and locations
- Plans for identifying potential participants including ensuring that effective referral systems are in place at participating clinics.
- Plans for tracking participants who are screened and potentially eligible for the study (e.g., maintenance of screening log)
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements
- Quality control/quality assurance quality control/quality assurance (QC/QA) procedures related to the above (if not specified elsewhere)
- Copies of recruitment worksheets, scripts, and other operational tools

4.2 Screening and Enrollment

Only after a pregnant woman has, as part of standard of care (outside of the study),

- been tested at least once for HIV with a positive result
- received HIV counseling
- been offered the local standard antiretroviral (ARV) regimen for prevention of mother to child transmission (pMTCT).

should she be asked to consent for screening and participation in HPTN 057. Each site will set up an internal referral system to ensure that women who may be eligible for study participation are referred to the appropriate study staff.

Staff may provide potential study volunteers basic information about the study and the participation requirements, however no protocol-specific screening procedures or assessments can be done until after a woman has undergone the screening informed consent discussion and signed the screening consent form. In addition, medical or other records from a non-study facility, e.g., documenting a woman's previous HIV test results, may not be accessed until the woman has consented to participation in screening for the study.

4.2.1 Assignment of Participant ID Numbers

Mothers are assigned a participant ID number (referred to as a “PTID”) when they provide informed consent for screening in the study. Infants are assigned a corresponding PTID at birth. See Section 12.5 for additional information on assignment of PTID.

4.2.2 Definition of Enrollment

The effective point of enrollment for a consenting eligible mother is presentation at the study facility for labor and delivery. The date of birth is considered Day 0 and all visits will be scheduled from that point forward. See Section 12.7 of this manual for additional information on visit timing and scheduling.

4.2.3 Screening and Enrollment Timeframe

Mothers can undergo informed consent for screening any time during pregnancy; however protocol-specified clinical and laboratory assessments must be performed during the last trimester (≥ 34 weeks gestation). Maternal screening visit procedures may be completed over the course of two or more visits, if needed. Women who meet the initial eligibility criteria and remain interested in participating in the study will receive intensive informed consent counseling for study enrollment.

Mothers who are determined to be ineligible will not be enrolled. Once a mother is found ineligible for any reason, the screening process is to be discontinued and no further assessments are to be performed. The reason for ineligibility must be documented on the screening log and in the individual participant’s source documents.

4.2.4 Screening and Enrollment Log

The DAIDS policy on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials requires study sites to document screening and enrollment activity on screening and enrollment logs. A sample log that may be adapted for local use at participating study sites is provided below in Fig 4-1. The logs must include the following information at a minimum: mother’s initials, mother’s and infant’s PTID, date of screening visits and, if enrolled, the date of enrollment. If not enrolled, the reason must be noted in the log.

Figure 4-1. Sample Screening and Enrollment Log

Mother’s Participant ID	Participant Initials	Date Screened/ Consent Signed	Date Enrollment Consent Signed	Mother Eligible? (y/n)	Infant’s Participant ID, if applicable	Enrollment Date	Cohort #	If not enrolled, specify reason

4.2.5 Screening and Enrollment Tracking

In accordance with HPTN policies, study staff will report the number of mothers screened, the number of mothers eligible, the number of mother/infant pairs enrolled into each cohort to the CORE Protocol

Specialist on a weekly basis and, when determined, the number of fully evaluable mother/infant pairs. The mode of delivery (vaginal, c-section) will also be reported for woman enrolled.

Cohorts 1 and 2 may be open for enrollment concurrently, however for logistical and procedural simplicity, Cohort 1 will enroll first. If the quota of C-sections has been met in Cohort 1, then eligible, consenting women scheduled to deliver by C-section may be enrolled in Cohort 2. If a woman missed her dose of study drug in Cohort 1 and remains eligible, then she and her baby could be enrolled in Cohort 2 which has no maternal dose.

Only consenting, eligible women who present at the study facility for labor and delivery will actually be enrolled in the study. Therefore, the point of enrollment will be the time of presentation at the clinic for delivery. If any exclusionary condition becomes known before or at the time of presentation for delivery, the woman will not be enrolled; however, eligibility assessments are not expected to be repeated at that point.

The Protocol Specialist will routinely distribute a consolidated report presenting accrual information from all sites to the Protocol Team as needed to monitor the accrual process. In addition, the SDMC will routinely report the number of mother/infant pairs enrolled each week based on data received and entered into the DataFAX study database.

As the study accrual period comes to an end at each site, care must be taken to manage the recruitment, screening, and enrollment process in order not to exceed the protocol-specified sample size of 80 across all sites. Potential participants must be informed that, although they may be screened and be eligible for the study, they may not be enrolled if the target sample size is reached before they deliver and are able to complete the enrollment process.

4.3 Informed Consent for Screening and Study Enrollment

Written informed consent must be obtained from all HPTN study participants prior to the performance of any protocol-specified screening or enrollment procedures and assessments.

Informed consent is a process by which an individual voluntarily expresses her willingness to participate in research, after having been informed of all aspects of the research that are relevant to her decision. Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process, with four key considerations — information exchange, comprehension, voluntariness, and documentation — each of which is described below. . See Section 4.8 of the International Conference on Harmonization Good Clinical Practice (GCP) Consolidated Guidance (ICH-E6) and the informed consent section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials for detailed guidance on the informed consent process and associated documentation requirements.

For this study, informed consent for screening is obtained from the mother for screening procedures and informed consent for study enrollment is obtained from the mother prior to delivery for study enrollment for her infant and herself. *Note: There are separate Screening and Enrollment Consent Forms for participation in Cohorts 1-3 and Cohort 4.* If the father of the infant is reasonably available at the study clinic, the study will also be thoroughly explained to him and his written informed consent obtained; however, the father's written consent is not required for enrollment of the mother or infant, unless otherwise directed by the Institutional Review Board/Ethics Committee IRB/EC overseeing research at the site. If the father is not available, this should be documented; however the specific reason need not be reported.

US regulations specify the elements of informed consent that must be conveyed to research participants through the informed consent process. It is the responsibility of the Investigator of Record (IoR), and his/her staff, to deliver complete and accurate information to potential research participants. Based on the technical and regulatory reviews that are completed as part of the HPTN protocol development and study activation processes, adequate assurance exists that once the site receives final approval for study initiation through an Activation Notice from the CORE, the IRB-approved site-specific informed consent form specifies all information required by the regulations.

Responsibility for informed consent does not end with preparation of an adequate informed consent form. It also is the responsibility of the IoR and designated study staff to perform the following:

4.3.1 Deliver Required Information in an Understandable Manner

As a starting point at the screening visit, designated study staff will assess participant literacy. If the participant is literate, staff will give her a copy of the informed consent form and any other IRB/EC-approved informational materials developed to complement the informed consent form (the responsible IRBs/ECs must approve such materials prior to use). Because many of the research concepts and terms may be unfamiliar even to literate women, the consent form must be reviewed very carefully with each potential volunteer. It is suggested that each paragraph be read aloud by the study staff member conducting the consent discussion and that the key points of each be emphasized, pausing after each paragraph to allow for questions and to probe for understanding. If the participant is not literate, staff will read the materials to her verbatim – pausing after each paragraph to emphasize key points and to allow for questions. A checklist highlighting key points may serve as a useful guide for reviewing the consent with the potential volunteer. For example, staff may note the main points described in each paragraph of the informed consent form, and ask if the participant has questions or concerns about each point. Staff should listen carefully to the questions and/or concerns expressed by the participant, and discuss these thoroughly and take as much time as needed to address each question and concern.

Note: If the participant is not literate, an impartial witness must be present during the entire informed consent discussion. As part of the documentation step described in Section 4.3.4, the witness will be asked to sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant. The ICH GCP guideline identifies an “impartial” witness as a person who is independent of the study and who cannot be unfairly influenced by people involved with the study. The CORE has received guidance from the US Food and Drug Administration’s GCP office stating that the witness need not be “totally unaffiliated with the study. It may be possible, for example, to designate a ‘subject advocate’ who would be available at each site.” Each site must specify its procedures for obtaining informed consent from illiterate persons in its SOP for obtaining informed consent. The SOP should define who may serve as the witness to the informed consent process. It is recommended that each site seek IRB/EC review and approval of these procedures.

4.3.2 Obtain Consent in a Setting Free of Coercion

During the informed consent discussion staff should take care not to overstate the possible benefits of the study, nor to understate the risks and to emphasize to the participant that the availability of medical care and other services routinely obtained from the recruitment site and/or research institution will not be affected by her decision.. Staff can encourage the participant to take as much time as she needs and to talk about her potential participation with others, if she chooses, before making a decision.

Note: If the participant is not literate, and therefore a witness is present during the entire informed consent discussion, care should be taken to minimize the perception of coercion due to the presence of the witness. For example, the purpose of having the witness present should be clearly explained to the participant, with emphasis on the fact that the witness is there as a protection for the participant, not as an agent of the study.

4.3.3 Confirm Participant Comprehension

The participant must not be asked to agree to take part in the screening/study or to sign or make her mark on the informed consent form until she fully understands the screening process/study. Study staff is responsible for implementing procedures to ensure that each participant understands the screening process and the study prior to signing/marketing the enrollment informed consent form and undertaking any screening or study procedures. Study staff should emphasize with potential volunteers aspects of the study that may be most challenging for them – for example, the fact she may need to remain in the hospital with her baby or return to the hospital frequently with her baby during the baby’s first of week life, the fact that the study staff may need to contact her at home, that the baby will have blood drawn multiple times during the first week of life, that she will need to bring the baby to the clinic many times over the course of the study. It is critical that volunteers fully understand what participation in the study entails before agreeing to participate.

One suggested approach to assessing comprehension is to use a “quiz” (either oral or written) or other assessment tool, which participants must complete prior to signing/marketing the informed consent form. Sample assessment tools for Cohorts 1- 3 and Cohort 4 are included in Tables 4-1a and 4-1b respectively at the end of this section. Another approach is to use open-ended questions to ascertain participant understanding during the informed consent discussion. For sites that choose to adopt tools such as those included at the end of this section, detailed use instructions must be specified in the site SOP for obtaining informed consent.

Regardless of the method used to assess comprehension, if the assessment results indicate misunderstanding of certain aspects of the study, review those aspects again until the participant fully understands them. If after all possible efforts are exhausted, the participant is not able to demonstrate adequate understanding of the study, do not ask her to sign/mark the informed consent form or continue screening for the study. Similarly, if the participant has concerns about possible adverse impacts on her or her baby if she were to take part in the study, or indicates that she may have difficulty adhering to the study requirements for her baby and/or herself, do not ask her to sign the informed consent form or continue screening for the study. If the potential volunteer has serious concerns about family members or others learning that she and her infant are in the study (e.g., because she will be coming frequently to the clinic) and she is not willing or able to discuss this with them in advance, she should not be asked to sign the consent and participate in the study.

4.3.4 Document the Process

US regulations require that informed consent be documented by "the use of a written informed consent form approved by the IRB/EC and signed and dated by the subject or the subject's legally authorized representative at the time of consent."

It is essential that the date signed on the screening consent form either precedes or coincides with the (first) study screening date. In addition, enter a note in the participant chart documenting that informed consent was obtained prior to the initiation of any study procedures. Finally, regulations require that participants be given a signed copy of the informed consent forms. If a participant opts not to receive a copy, document this in a chart note.

Signatures on the consent forms must be the legal name and not include fabricated or falsified names. Sites are not required to verify a person's legal name, however, if the site becomes aware that a person has not used his/her legal name, then staff must follow the instructions for this situation in the DAIDS SOP for Source Documentation.

Initials cannot be used for the family name. Use of initials for first names is discouraged but not prohibited as long as it is acceptable per the policy of the local institution. The consent must be dated by the person signing the form; it is not acceptable for study staff to complete the date. All entries must be in ink.

Note: If the participant is not literate, the witness who was present during the informed consent discussion must sign and date the informed consent form to attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant. If the participant cannot write her name or the date, this should be documented in the research record, in a chart note and/or on a face sheet or other documentation tool. In addition, the participant printed name, signature, and signature date blocks on the informed consent form should be completed as follows:

- *The study staff member who completed the informed consent discussion with the participant should enter the participant's name below the "participant's printed name" block (the line for the participant to write her name should be left blank), together with an initialed and dated note documenting the initials of the person who made the entry and the date of the entry and noting that the participant could not sign for herself.*
- *The participant should make her mark in the "participant's signature" block.*
- *The "participant signature date" block should be left blank and date should be recorded below the line by the person conducting the consent discussion, and initialed and dated.*

The DAIDS SOP for Source Documentation (Appendix B) provides detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the DAIDS SOP must be met. To meet the suggestions listed in the DAIDS SOP, site staff may consider the use of an informed consent "coversheet" similar to the example included in Table 4-2 at the end of this section.

The above describes aspects of obtaining informed consent from study participants prior to initiating their involvement in the study. Given the ongoing nature of informed consent, key elements of informed consent also should be reviewed at all study follow-up visits. At these visits, study staff should review key elements of informed consent with the participant, focusing on the remainder of their study participation.

As a condition for study activation, each study site must establish an SOP for obtaining informed consent from potential study participants. This SOP should reflect all of the information provided in this section and minimally should contain the following elements:

- Procedures for ascertaining participant identity and age
- Procedures for ascertaining participant literacy
- Procedures for providing all information required for informed consent to the mother and father (if available)
- Procedures for ascertaining participant comprehension of the required information
- Procedures to ensure that informed consent is obtained in a setting free of coercion and undue influence

- Procedures for documenting the informed consent process
- Considerations and requirements for illiterate participants, including specification of who may serve as a witness to the informed consent process
- Considerations and requirements for obtaining consent for continued/infant child study participation after mother's death, including specification of who may serve as a legal guardian or legally acceptable representative
- Storage locations for blank informed consent forms
- Storage locations for completed informed consent forms
- Procedures (e.g., color-coding) to ensure that the two study informed consent forms —enrollment and specimen storage — are easily distinguished and used appropriately
- Procedures for implementing a change in the version of the informed consent form
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements
- QC/QA procedures related to the above (if not specified elsewhere)
- Copies of all forms, worksheets, checklists, etc. to be used during the informed consent process with instructions

4.4 Consent for Infant's Continuation in the Study after Maternal Death

US Federal regulations require that consent be obtained from a legal guardian for continued study participation in the event that a child's parents are deceased or otherwise unavailable. If a mother in HPTN057 dies and the father has not already provided written informed consent, all study-specific assessments and data collection must be ceased until written informed consent is obtained from someone considered a guardian according to the local laws and the IRBs/ECs overseeing the research at that site. Care for the infant can and should continue to be provided as necessary. Sites are expected to seek clarification in advance from their IRBs/ECs on how to handle obtaining appropriate consent for an infant's continuation in the study in the event that the mother dies, particularly given the potential sensitivities regarding disclosure of the mother's HIV status in explaining the purpose of the study. Each site is expected to work with their IRBs/ECs to agree in writing on exactly how this is to be handled for this study. If the site chooses to develop a consent form for this specific purpose, it must be approved by the IRBs/ECs and provided to the DAIDS RCC (through the CORE) prior to actual use.

4.5 Storage of Consent Forms

All consent forms (screening and study enrollment) completed during the screening process must be retained even if the mother was not enrolled in the study. It is acceptable for sites to maintain consents in a file separate from a subject's research record and to separate those for enrolled women from those screened but not enrolled, provided that the site does this consistently for all subjects. Sites should maintain any subsequent versions of the consent in the same manner.

4.6 Eligibility Determination

Documentation to address each of the protocol's inclusion and exclusion criteria must be present in the individual's research record. It is the responsibility of the site IoR and other designated staff to ensure that only mothers who meet the study eligibility criteria are enrolled in the study. Maternal inclusion and exclusion criteria can be found in Protocol Section 3.1 and 3.2 respectively. Criteria for initial infant dosing can be found in Protocol Section 3.3 and 3.4. As a condition for study activation, study sites must establish an SOP that describes how study staff will fulfill this responsibility. This SOP minimally should contain the following elements:

- Eligibility determination procedures for mothers including:

- ◆ During-visit eligibility assessment procedures
- ◆ Post-visit eligibility assessment and confirmation procedures
- ◆ Final confirmation and sign-off procedures prior to enrollment
- ◆ Documentation
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements
- QC/QA procedures related to the above (if not specified elsewhere)

Table 4 -1a.**Sample Informed Consent Assessment Tool for Enrollment in HPTN 057 (Cohorts 1- 3)**

		True	False
1	This study is part of the regular medical care offered here at [clinic name].	<input type="checkbox"/>	<input checked="" type="checkbox"/>
2	One purpose of this study is to find out if giving tenofovir to mothers during labor and babies very soon after birth is safe.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
3	You and your baby will be in the study for a year.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
4	All mothers will receive the study drug.	<input type="checkbox"/>	<input checked="" type="checkbox"/>
5	If you join this study you will not receive the standard drugs used to prevent passing HIV to your baby, instead you will only receive the drug we are studying called tenofovir.	<input type="checkbox"/>	<input checked="" type="checkbox"/>
6	If you join this study and are assigned to group 1 blood will be taken from your baby 5 times during the first week of birth	<input checked="" type="checkbox"/>	<input type="checkbox"/>
7	If you join this study and are assigned to group 2 or 3 blood will be taken from your baby 14 times during the first week after birth.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
8	If you join this study and are assigned to group 2 or 3 your baby will receive the study syrup at this clinic at birth and 3 and 5 days after birth.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
9	You will be able to choose which group that you will be in.	<input type="checkbox"/>	<input checked="" type="checkbox"/>
10	Participants' study records will be available to everyone at the [clinic name].	<input type="checkbox"/>	<input checked="" type="checkbox"/>
11	Being in this study could cause problems for study participants with their partners or family members.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
12	If you decide not to join this study, you can still come to the [clinic name] for medical care.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
13	If the study staff finds that you have any medical problems, they will refer you to available sources of medical care for those problems.	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Table 4 -1b.**Sample Informed Consent Assessment Tool for Enrollment in HPTN 057 (Cohort 4)**

		True	False
1	This study is part of the regular medical care offered here at [clinic name].	<input type="checkbox"/>	<input checked="" type="checkbox"/>
2	One purpose of this study is to find out if giving tenofovir to mothers during labor and babies very soon after birth is safe.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
3	You and your baby will be in the study for a year.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
4	All mothers will receive the study drug.	<input type="checkbox"/>	<input checked="" type="checkbox"/>
5	If you join this study you will not receive the standard drugs used to prevent passing HIV to your baby, instead you will only receive the drug we are studying called tenofovir.	<input type="checkbox"/>	<input checked="" type="checkbox"/>
6	If you join this study and are assigned your baby will be given study syrup once a day for 7 days.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
7	If you join this study and are assigned blood will be taken from your baby 14 times during the first week after birth.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
8	Participants' study records will be available to everyone at the [clinic name].	<input type="checkbox"/>	<input checked="" type="checkbox"/>
9	Being in this study could cause problems for study participants with their partners or family members.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
10	If you decide not to join this study, you can still come to the [clinic name] for medical care.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
11	If the study staff finds that you have any medical problems, they will refer you to available sources of medical care for those problems.	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Table 4-2. Sample Informed Consent Coversheet for HPTN 057

Participant Name:	
Type of consent discussion:	<input type="checkbox"/> Screening <input type="checkbox"/> Enrollment
Date of informed consent discussion:	
Time of informed consent discussion:	
Name of study staff person completing informed consent discussion (and this coversheet):	
Is the potential volunteer literate?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ If no, an impartial witness should be present during the entire informed consent discussion. Refer to informed consent SOP for specific instructions.
Did the father undergo the informed consent discussion and sign the consent form?	<input type="checkbox"/> Yes <input type="checkbox"/> Not available
Was a copy of the informed consent form given to the participant?	<input type="checkbox"/> Yes <input type="checkbox"/> No, refused to accept

Notes/Comments (not documented elsewhere):