

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 2) and detailed in the visit checklists (Section 6). Additional instructions for clinical and laboratory procedures can be found in Sections 9 and 10 of this manual, respectively. Refer to Appendix K for instructions regarding participants enrolled under version 2.0 of the protocol.

4.1 Recruitment and Target Enrollment

Approximately 1670 mother/infant pairs will be enrolled across all of the sites in order to randomize a target of 1500 infants at six weeks. It is anticipated that each study site will enroll approximately 25 to 35 mother/infant pairs per month over 18 to 24 months.

Site staff are 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 monthly accrual goals
- Recruitment methods and locations
- Plans for identifying potential participants including ensuring that effective referral systems are in place at participating clinics and ensuring that thorough infant feeding counseling is provided
- Plans for proactive internal monitoring of recruitment progress and strategy
- 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
- QC/QA procedures related to the above (if not specified elsewhere)
- Attached 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 and
- received thorough infant feeding counseling and subsequently indicated her intent to breastfeed

should she be asked to consent for screening and participation in HPTN 046. 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. Each site must also ensure that the infant feeding counselors have been trained in accordance with WHO and local MOH guidelines.

Staff may provide potential study volunteers basic information about the study and the participation requirements, however no protocol-specific procedures or assessments can be done until after a woman has undergone the complete informed consent discussion and signed the enrollment 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 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 enrollment in the study. Infants are assigned a corresponding participant ID number at birth. See Section 12.5.1 for additional information on assignment of participant ID numbers.

4.2.2 Definition of Enrollment

The mother/infant pair must be present in the clinic in order to be enrolled. After final eligibility of the both the mother and the infant is confirmed, the effective point of enrollment for a mother/infant pair is when their PTIDs are entered into the enrollment log and the Open-Label Nevirapine Prescription is signed by the prescribing clinician.

4.2.3 Screening and Enrollment Timeframe

Mothers can be screened for enrollment during the third trimester of pregnancy through 7 days post-delivery. Maternal screening visit procedures may be completed over the course of two or more visits, if needed. Mothers who are initially screened at or after labor and delivery will only have the labor and delivery clinical evaluations and blood draw completed as described in the visit checklists in Section 6. Infants born to eligible mothers must be assessed for eligibility and enrolled on or before Day 7 after birth, with the day of birth considered Day 0. For example, an infant born on Sunday could be enrolled anytime through the end of the day on the following Sunday. Enrolled infants are to begin open-label nevirapine (NVP) on any day from Day 3 through Day 7 of life. See Section 8 of this manual for dosing and administration procedures for open-label NVP.

Once a mother and/or her infant are 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 subject’s source documents.

4.2.4 Screening and Enrollment Log

The DAIDS SOP for Essential Documents (Appendix A) requires study sites to document HPTN study screening and enrollment activities on a screening and enrollment log. This log documents the identification of subjects who enter pre-trial screening and the chronological enrollment of subjects. A sample log that may be adapted for local use at participating study sites is provided in Appendix D. The logs must include the following information at a minimum: mother’s initials, mother’s and infant’s participant ID number, date of screening visits and, if enrolled, the date enrolled. If the infant is not enrolled the reason must also be noted in the log.

4.2.5 Screening and Enrollment Tracking

In accordance with HPTN policies, study staff will report the number of mothers screened for enrollment, the number of mothers eligible for enrollment, the number of mother/infant pairs enrolled into the study and the number of infants randomized, to the CORE Protocol Specialist on a weekly basis. 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 1500 infants to be randomized across all sites. Particularly in the last 3 months of accrual, enrollment must be monitored closely, and potential participants must be informed that although they may screen 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. This may be difficult to explain to women — especially those who are very interested in taking part in the study — therefore all sites are advised to work with their local community advisory board (CAB) members to develop strategies to address this issue either prior to or soon after study start-up.

4.3 Informed Consent for Initial Screening and Enrollment under Version 3.0

Note: Procedures for obtaining informed consent from participants enrolled and randomized under Version 2.0 to continue participation under Version 3.0 may be found in Appendix K.

Written informed consent must be obtained for all HPTN study participants prior to the performance of any protocol-specified screening or enrollment procedures and assessments. For this study, informed consent is obtained from the mother for screening and enrollment of her infant and herself.

Father's consent: 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 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.

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 ICH GCP guideline and the informed consent section of the DAIDS SOP for Source Documentation (Appendix B) for detailed guidance on the informed consent process and documentation requirements.

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, 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 Investigator 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, assess participant literacy. If the participant is literate, give her a copy of the informed consent form to read. Also provide the participant with other IRB/EC-approved informational materials developed to complement the informed consent form, if any (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 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, 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, you 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. Listen carefully to the questions and/or concerns expressed by the participant, and discuss these thoroughly. Take as much time as needed to address each question and concern.

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, 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, take care to not overstate the possible benefits of the study, nor to understate the risks. Also 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 whether or not to take part in the study. 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 are 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 will be given a study drug to take home to give the baby, that there is a difference between the open-label drug and study drug, the fact that the study staff may need to contact her at home, 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. A sample assessment tool is included in Table 4-1 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 would be giving the baby study drug every day or coming frequently to the study 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 documented on the 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 the instructions provided for this situation in the DAIDS SOP for Source Documentation must be followed.

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 for another signer. 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 “participant’s printed name” block should be left blank and the name should be recorded below the line by the person conducting the consent discussion, and initialed and dated. The participant chart should include documentation that the participant could not sign for him/herself (e.g., documentation in the informed consent coversheet).*
- *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. In order to also meet some of 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. For example, at the 6 month visit, the discussion might focus on the fact that the dosing portion of the study has ended so scheduled visits will occur less frequently during the remaining follow-up period.

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:

- A procedure for assuring that the informed consent process was administered by someone who did not provide infant feeding options counseling
- 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)
- Attached copies and instructions for use of all forms, worksheets, checklists, etc. to be used during the informed consent process

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 HPTN 046 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. (*Note: if the mother dies, study drug will be immediately discontinued, therefore continued participation includes only follow-up visits and assessments.*) 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 prior to actual use.

4.5 Informed Consent for Specimen Storage

Storage of specimens remaining after trial completion is optional for each site. If a site chooses to store leftover biological specimens after all of the protocol-specified assessments and quality control procedures are completed, separate written informed consent must be obtained from each participant. This consent may be obtained after a woman is enrolled in the study (i.e., it need not be done at screening). If the father of the infant is reasonably available, his consent should also be sought. If the father is not available, this should be documented; however the specific reason need not be reported. Mothers may choose to not have their or their infants' specimens stored for possible future research testing and still enroll/remain in the study. To facilitate completion of CRFs at the end of the study and management of specimens, sites should keep a record that can be used to ascertain and verify who signed the consent for storage of leftover specimens. Note: Unless otherwise directed by the IRB/EC, participants who were enrolled under Version 2.0 of the protocol and consented for specimen storage under that version need not be re-consented for specimen storage under Version 3.0, as there was no substantive change in that consent form from Version 2.0 to Version 3.0.

4.6 Storage of Consent Forms

All consent forms 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.

4.7 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 Investigator of Record and other designated staff to ensure that only mothers and infants who meet the study eligibility criteria are enrolled in the study. 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 both mothers and infants, including:
 - During-visit eligibility assessment procedures
 - Post-visit eligibility assessment and confirmation procedures
 - Final confirmation and sign-off procedures prior to enrollment/randomization
 - 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)

4.7.1 Maternal Eligibility Criteria

Mothers must meet all of the following criteria to be eligible for the study:

- At least 18 years of age
- Willing and able to provide study informed consent
- Third trimester of pregnancy or on or before day 7 after delivery
- HIV-infected, as evidenced by at least 1 positive EIA and 1 positive WB, or at least 1 positive rapid test and 1 positive WB.
- No serious medical condition that would interfere with participation in the study (e.g. a condition that would prevent breastfeeding or adherence to the follow-up schedule), as judged by the on-site clinician.
- Intend to breastfeed
- If not already delivered: Intend to deliver at a facility where the study is based

Note: If documented evidence of the mother's HIV status by 1 positive EIA or 1 positive rapid test is not available as part of standard of care HIV testing at the study clinic, then testing will be performed after study informed consent has been obtained and prior to enrollment. Confirmatory testing by Western blot is required after informed consent is obtained, regardless. When a previous (non-study) HIV test result is used to document a woman's eligibility for study participation, as per the study protocol, the original record or a certified copy must be available in the subject's research record.

Note: Women who are receiving or have received antiretrovirals (including NVP) for treatment or for prevention of MTCT are eligible.

Note: Careful enrollment of the right participants is essential for ensuring a high level of retention later in the study. Study staff should be judicious in participant enrollment rather than enrolling anyone who meets eligibility criteria. Potential participants who seem ambivalent about study participation should most likely not be enrolled.

Note: Mothers will be considered enrolled in the study at the point of infant enrollment. Mothers of infants who are not enrolled will not be considered enrolled in the study.

4.7.2 Infant Enrollment Criteria

Infants must be enrolled on or before 7 days post delivery, with the day of birth considered Day 0. Infants must meet the following criteria for eligibility for enrollment:

- Born to an HIV-infected mother who is eligible and has consented to take part in this study
- HIV-1 DNA PCR negative from a specimen obtained on or before Day 7 of life (quantitative HIV-1 RNA PCR may be used if HIV-1 DNA PCR is not available).
- Birth weight of at least 2000 gm
- Able to breastfeed (i.e., mother and infant alive with no condition apparent that would preclude breastfeeding)

Infants who meet any of the following criteria will be excluded from enrollment:

- ALT from birth specimen is Grade 2 or higher
- Hemoglobin, absolute neutrophil count or platelet count from birth specimen is Grade 3 or higher
- Skin rash Grade 2B (urticaria)
- Skin rash Grade 3 or above
- Confirmed or suspected clinical hepatitis, defined as clinical signs and symptoms of clinical hepatic dysfunction including enlarged liver (>4 cm below right costal margin), hepatic tenderness and ascites
- Serious illness or condition that would prohibit compliance with study procedures as judged by site clinician.

Note: In the case of a multiple birth, infants will be included in the study only if both/all are eligible. If only one infant of a multiple birth is alive, he/she may be enrolled if he/she otherwise meets all of the criteria.

Table 4-1: Sample Informed Consent Assessment Tool for Enrollment in HPTN 046

		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 nevirapine syrup to babies every day from 6 weeks of life to 6 months will help stop them from becoming infected with HIV from breast milk.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
3	All infant participants enrolled in the study will receive NVP or NVP placebo from 6 weeks of age to 6 months.	<input type="checkbox"/>	<input checked="" type="checkbox"/>
4	Mother and infant participants will have study visits every three months.	<input type="checkbox"/>	<input checked="" type="checkbox"/>
5	Infant participants will be tested for HIV at least 3 times during the first 6 weeks of the study.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
6	Mother participants will provide breast milk specimens while breastfeeding.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
7	If you join this study, you and your infant must stay in the study for as long as the study nurse says.	<input type="checkbox"/>	<input checked="" type="checkbox"/>
8	Participating mothers will be expected to give NVP to their infants once a week for the first 6 weeks of the infants' life.	<input type="checkbox"/>	<input checked="" type="checkbox"/>
9	Every infant will receive nevirapine syrup every day for the first 6 weeks of life.	<input checked="" type="checkbox"/>	<input 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	Study participants can get condoms and HIV counseling from the study staff at any time.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
14	If the study staff find 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 046

Participant Name:	
Type of consent discussion:	<input type="checkbox"/> Study Enrollment <input type="checkbox"/> Specimen Storage
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):
