IMPAACT 2009

Pharmacokinetics, Feasibility, Acceptability, and Safety of Oral Pre-Exposure Prophylaxis for Primary HIV Prevention during Pregnancy and Breast Feeding in Adolescents and Young Women and their Infants

Manual of Procedures
PK Component

Version 1.0
3 July 2018
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1.0 Study Overview

IMPAACT 2009 is a parallel, observational cohort study of the pharmacokinetics (PK), feasibility, acceptability, and safety of oral pre-exposure prophylaxis (PrEP) for primary HIV prevention during pregnancy and postpartum in adolescents and young women (ages 16 – 24) and their infants. This study is comprised of two components:

1. **PK Component**: Will establish the plasma drug concentrations associated with daily directly observed oral PrEP during pregnancy and postpartum.
2. **PrEP Comparison Component**: Will characterize adherence over time among women who initiate once daily oral PrEP during pregnancy and continue in the first six months following delivery, and to compare pregnancy outcomes among women who take PrEP and women who decline PrEP during the antenatal period.

This Manual of Procedures (MOP), **corresponds to the PK Component**, which will precede the PrEP Comparison Component (refer to protocol, Figure 1: Overview of Study Design). An amended version of this MOP will be made available prior to implementation of the PrEP Comparison Component.

**Sample Size**: Approximately 40 women (20 per group) to achieve at least 30 evaluable women (15 per group) and their infants.

**Population**: HIV-uninfected pregnant women 16 – 24 years of age and their infants will be enrolled in two groups:

- **Group 1**: Enrolled during singleton pregnancy at 14 – 24 weeks’ gestation
- **Group 2**: Enrolled postpartum within 6 – 12 weeks after delivery

**Study Intervention**: Fixed dose combination of 200 mg emtricitabine (FTC) and 300 mg tenofovir disoproxil fumarate (TDF) administered once daily under direct observation for 12 weeks.

**Study Duration**: Approximately nine months total for this component. Women will be accrued over a three-month period (from the date of first enrollment) and retained in follow-up 12 weeks. Analysis of PrEP drug level will be completed within three months after the last participant follow-up visit.

2.0 Preparing for the Study

This study will be conducted at the IMPAACT clinical research sites (CRSs) listed below, which were selected by the Protocol Team based on review and approval of site selection materials. Refer to the IMPAACT Manual of Procedures for additional details regarding the site selection process:


A copy of the approved site selection materials should be maintained in each site’s study-specific essential document files.
2.1 Investigator Responsibilities

IMPAACT 2009 must be conducted in accordance with the United States (U.S.) Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice (GCP). The Division of AIDS (DAIDS) policies on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials are useful for interpreting and operationalizing the regulations and guidelines in accordance with DAIDS expectations. These policies are available at the following web site and must be followed throughout implementation of IMPAACT 2009:

https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

IMPAACT 2009 also must be conducted in accordance with the IMPAACT Manual of Procedures and all site-specific regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. Copies of all applicable regulations, policies, and guidelines should be maintained in on-site essential document files. The IMPAACT Manual of Procedures is available at:

http://impaactnetwork.org/resources/policies-procedures.htm

The Investigator of Record (IoR) at each site must sign an FDA Form 1572 to formally indicate his or her agreement to conduct the study in accordance with the protocol and all applicable regulations, policies, and guidelines. The obligations and responsibilities assumed by the IoR when signing the FDA Form 1572 are listed on the form, which is available on the DAIDS Regulatory Support Center (RSC) website:

http://rsc.tech-res.com/clinical-research-sites/protocol-registration/form

IoRs may delegate their obligations and responsibilities for conducting IMPAAACT 2009 to other study staff; however, delegation does not relieve the IoR of his or her ultimate responsibility for all study procedures performed and all study data collected. Delegation of IoR responsibilities must be formally documented throughout the period of study implementation.

Consistent with the regulations, guidelines, and policies cited above, the IoR at each site must obtain all applicable drug regulatory and ethical review approvals for IMPAAACT 2009 prior to study initiation; the
IoR must also maintain these approvals in good standing throughout the period of study implementation. With regard to drug regulatory authorities (DRAs), the IoR must complete initial and continuing submissions in accordance with DRA policies. With regard to institutional review boards and ethics committees (IRBs/ECs), further guidance on initial and continuing review requirements is available in 45 CFR 46 and the ICH GCP guidance, as well as on the web site of the U.S. Office for Human Research Protections (OHRP):

http://www.hhs.gov/ohrp/

All sites are encouraged to request an acknowledgement of receipt for all documents submitted to their DRAs and IRBs/ECs and to request that DRAs and IRBs/ECs note the effective and expiry dates of all approvals. Because IMPAACT 2009 involves pregnant women, fetuses, and infants, IRBs/ECs must consider the potential risks and benefits of the study for mothers and children as described in protocol Section 13.2. Complete documentation of all correspondence to and from all responsible DRAs and IRBs/ECs (i.e., complete copies of all submissions, responses, and approvals) must be maintained in on-site essential document files. All submission letters should list the date of the submission, the contents of the submission, and the version number and/or version date of each document submitted.

2.2 Protocol Registration

The IMPAACT Operations Center will notify the DAIDS Protocol Registration Office (PRO) that DAIDS-approved sites selected by the Protocol Team for participation are permitted to submit for protocol registration for the study. After obtaining all required DRA and IRB/EC approvals, each participating study site is responsible for submitting documentation of the approvals, and other required documents, to the DAIDS Protocol Registration Office (PRO). Further information on the protocol registration process can be found in protocol Section 13.2 and in the DAIDS Protocol Registration Manual, which is available at:

http://rsc.tech-res.com/clinical-research-sites/protocol-registration/policy-manual

Upon confirming receipt of all required documentation, the PRO will issue an Initial Registration Notification that indicates successful completion of the process. Site staff are responsible for maintaining documentation of all submissions for the study, along with all associated approvals, notifications and other correspondence from the PRO. Sites must obtain an Initial Registration Notification for protocol Version 1.0, and Letter of Amendment (LoA) #1 as a condition for study activation (described below).

2.3 Site-Specific Study Activation

Prior to conducting any study procedures, each site must obtain all required approvals (as described above) and must complete study-specific activation procedures specified by the Protocol Team. To help ensure site readiness for study initiation, the Protocol Team has specified a set of study activation requirements that must be met to obtain approval to begin study implementation. These requirements are listed on the IMPAACT 2009 Site-Specific Study Activation Checklist, which is available upon request from the IMPAACT Operations Center Clinical Trial Specialists.

Any questions related to the study activation process should be directed to the IMPAACT Operations Center. On a site-by-site basis, when all activation requirements have been met, the Operations Center will issue a site-specific study activation notice. At each site, no study procedures may be performed prior to receipt of the activation notice.
3.0 Study Resources

This section specifies the resources available to IMPAACT 2009 study site staff, including study-related communication and informational resources, the Data Management Center (DMC) IMPAACT Portal, and other essential documents.

3.1 Study-Related Information and Communications

All IMPAACT 2009 visits and procedures must be conducted in accordance with the study protocol. The purpose of this Manual of Procedures (MOP) is to supplement the protocol, not to replace or substitute for it. If this manual is inconsistent with the protocol, the specifications of the protocol take precedence. Please notify the IMPAACT Operations Center Clinical Trial Specialists of any such inconsistencies.

The Protocol Team has developed study-specific contacts for various types of issues and questions, as described in Figure 3-1. For issues and questions directed to the Protocol Team, a response from the appropriate team member can generally be expected within 24 hours.

Figure 3-1
Study-Related Communications

<table>
<thead>
<tr>
<th>Topic</th>
<th>Contact</th>
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<tbody>
<tr>
<td>Adding site staff to Protocol Team email group (<a href="mailto:IMPAACT.prot2009@fstrf.org">IMPAACT.prot2009@fstrf.org</a>)</td>
<td>User Support <a href="mailto:user.support@fstrf.org">user.support@fstrf.org</a> (include “IMPAACT 2009” in the subject line of your email message)</td>
</tr>
<tr>
<td>Any aspect of protocol interpretation or study implementation not listed below</td>
<td>IMPAACT 2009 Protocol Team <a href="mailto:IMPAACT.team2009@fstrf.org">IMPAACT.team2009@fstrf.org</a> (for triage to other team members as needed)</td>
</tr>
<tr>
<td>Clinical, adverse event, and study drug management issues</td>
<td>IMPAACT 2009 Clinical Management Committee <a href="mailto:IMPAACT.2009CMC@fstrf.org">IMPAACT.2009CMC@fstrf.org</a></td>
</tr>
<tr>
<td>Participant eligibility, potential enrollment of an ineligible participant, and/or deviation from protocol requirements for eligibility determination and/or enrollment</td>
<td>IMPAACT 2009 Clinical Management Committee <a href="mailto:IMPAACT.2009CMC@fstrf.org">IMPAACT.2009CMC@fstrf.org</a></td>
</tr>
</tbody>
</table>
| Data management questions, including case report form completion issues | DMC Protocol Data Managers
Laura Smith, lsmith@fstrf.org
Ben Johnston, johnston@fstrf.org |
| Co-enrollment issues                                                | IMPAACT 2009 Clinical Management Committee IMPAACT.2009CMC@fstrf.org    |
| DMC Portal and Medidata Rave user account issues                    | User Support (FSTRF) user.support@fstrf.org
or by phone: +716-834-0900 x7302                                        |
| Subject Enrollment System                                           | DMC Randomization Support Office rando.support@fstrf.org
or by phone: +716-834-0900 x7301                                          |
| Study drug (other than study drug orders)                           | Protocol Pharmacist
Kelly Parsons, Pharm D, BCPS
kelly.parsons@nih.gov
or by phone: 301-761-6659                                                  |
Active communication is expected between site staff and the IMPAACT 2009 Clinical Management Committee (CMC). The IMPAACT 2009 CMC is composed of study team members who have been designated to receive and reply to clinical management questions and notifications; see protocol Section 7.1.2. When submitting questions and notifications to the CMC, please address each of the points listed in Figure 3-2 to help ensure that CMC members have adequate information to respond in a timely manner. Always retain a copy of correspondence with the CMC in the relevant participant’s study chart.

**Figure 3-2**
Communications with IMPAACT 2009 Clinical Management Committee

*Questions and notifications for IMPAACT 2009 CMC: Please copy and paste this listing into the body of your email message to IMPAACT.2009CMC@fstrf.org to help ensure that all required information is included.*

- Include the protocol number and PID in the subject line of your email.
- Site name and number:
- Name of person submitting query:
- PID(s):
- PK Component: Group 1 or Group 2
- Query is for consultation on (choose one):
  - Eligibility or enrollment (describe in case description)
  - DOT
  - AE or toxicity management (specify severity grade in case description)
  - Administration of prohibited medications (specify medication/describe in case description)
  - Positive maternal or infant HIV test results
  - Evaluability of maternal participant in PK component
  - Other (specify in case description)
- Current week on study:
- Case description and question or notification for CMC:

*File a copy of the email exchange in the participant’s study chart.*
The IMPAACT 2009 protocol also details the circumstances in which IoRs must consult with the CMC. All protocol requirements must be followed. For ease of reference, a summary of issues requiring consultation with the IMPAACT 2009 CMC, and those for which consultation is available but not required, is provided below in Figure 3-3. IoRs are also encouraged to contact the CMC with any other issues, questions, or concerns related to study drug regimens for study participants.

Figure 3-3
Situations that Require Consultation with the IMPAACT 2009 CMC

For details on toxicity management, refer to the following appendices in the protocol:
- Appendix IV: General Management Guidelines for Maternal Toxicities
- Appendix V: General Management Guidelines for Maternal Reduced Creatinine Clearance

Study Implementation
- Requests for co-enrollment in other studies.
- Evaluability of maternal participant in PK component with more than three consecutive missed doses.
- A participant is administered any prohibited medications as described in protocol Section 5.5. The CMC must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited medications are administered.
- Investigator or designee determines continued participation in the study would be unsafe or otherwise not in the best interest of the participant.
- Positive maternal or infant HIV test results (initial positive test results and confirmatory test results)

General Toxicities
- Consultation with the CMC is required for the following General Toxicities:
  - Any event resulting in a change in the administration of the study product
  - Clinical Grade 3 or 4 toxicity
  - Laboratory Grade 3 or 4 (confirmed with repeat test)
- Consultation with the CMC is available, but not required, for Grade 1 or Grade 2 clinical or laboratory events

Maternal Reduced Creatinine Clearance
- <50ml/minute or >50% decrease from baseline test result (confirmed with repeat test)

3.2 Data Management Center (DMC) IMPAACT Portal

The IMPAACT Portal of the DMC website provides information, documents and tools to assist site staff with the data management aspect of conducting IMPAACT studies, including the eCRF Completion Guide which includes the Case Report Forms (CRFs) and forms instructions, as well as the data collection forms schedules, Forms Management Utility for participant questionnaires, Participant Calendar, and Subject Enrollment System (SES). The IMPAACT Portal can be accessed from the Frontier Science and Technology Research Foundation (FSTRF) webpage at: https://www.frontierscience.org/

Site staff members apply for access to the Portal by submitting a registration form located on the Frontier Science and Technology Research Foundation (FSTRF) home page. All requests for Portal access are subject to review and verification by User Support before processing. The site leader or site coordinator will be contacted by the DMC to ensure legitimate affiliation of the applicant. To request for DMC IMPAACT Portal access complete the form located at:

https://www.frontierscience.org/apps/cfmx/apps/common/register/index.cfm
Confirmation of registration will be sent via email from User Support. Click on the IMPAACT project link to enter the project website. A log-in screen appears. Enter your username (format: lastname.firstname) and the password that you set up when you registered for DMC web access.

For clinical user support, send an email message to impaact.support@fstrf.org or call +1 (716) 834-0900 x 7302. If you experience problems, or have questions about the IMPAACT portal in the Frontier Science website, please contact the Webmaster at webmaster@fstrf.org and include a detailed description of your question or the problem you encountered.

3.2.1 Electronic Case Report Form (eCRF) Completion and Data Entry

The DMC has developed an eCRF completion guide to assist site staff in the accurate completion of electronic Case Report Forms (eCRFs) used for DAIDS-sponsored Clinical Trials. Additionally, a print matrix of the 2009 eCRFs is available. The 2009 eCRF Completion Guide and the 2009 Print Matrix are located in the DMC IMPAACT Portal under the Site Support heading and the Medidata Rave Resources link. The eCRF completion guide and Print Matrix may be used as guides for source documentation purposes.

The eCRF completion guide contains the data collection forms schedules and all of the eCRFs with instructions and help text. These documents outline standards and guidelines which, when followed, will result in fewer queries, shorter delinquency lists, and most importantly, straightforward and timely analyses.

The participant questionnaires have been posted in English, and other needed language translations have been posted in the Forms Management Utility, located on the DMC IMPAACT Portal under the Case Report Form heading.

Additionally, the eCRFs may also be accessed through the Medidata RAVE system.

3.3 Study Webpage

A variety of IMPAACT 2009 study-related materials and information can be found on the study-specific webpage: http://www.impaactnetwork.org/studies/IMPAACT2009.asp

Resources available on this site include:

- Current version of the protocol, including any Clarification Memoranda (CMs) and/or Letters of Amendment (LoAs)
- Study contacts
- List of participating sites
- Current study implementation materials, including this Manual of Procedures (MOP) and the Laboratory Processing Chart (LPC)
- Study training materials

4.0 Participant Accrual

4.1 Overview

Up to 40 women and their infants will be enrolled into two groups (20 women per group) in the PK Component to achieve at least 30 evaluable women (15 per group). Group 1 is defined as women who
enroll during singleton pregnancy at 14-24 week’s gestation; and Group 2 is defined as women who enroll postpartum within 6-12 weeks after delivery.

Both groups will be accrued simultaneously, and accrual is expected to be completed within three months, beginning from the date the first participant is enrolled. A maternal participant is considered evaluable if she meets the criteria specified in protocol Section 9.1.1

Each study site should have a standard operating procedure (SOP) for participant accrual on file. Sites will also be required to have study-specific SOPs for participant recruitment and implementing directory observed therapy (DOT) on file prior to site activation. All sites are responsible for following these SOPs and for updating them if needed to meet site-specific accrual projections throughout the study accrual period.

For each site, accrual will begin after all required approvals are obtained and a site-specific study activation notice is issued by the IMPAACT Operations Center, as described in Section 2.3, above. Once accrual is initiated, the SDMC will report data on accrual, missed weekly visits, missed PrEP doses, doses with inadequate source documentation of direct observation, etc. to the CMC at least monthly; see protocol Section 9.1.5 for additional information.

Throughout the accrual period, the Protocol Team will review accrual from each site to determine whether accrual targets should be adjusted across sites to achieve the study objectives most efficiently. Findings and recommendations from these reviews will be communicated to all sites, and all sites will adjust their accrual efforts accordingly. Similar adjustments may be made after the IMPAACT Study Monitoring Committee (SMC) reviews of the study, which are expected at least once annually.

4.2 Participant Recruitment, Screening and Enrollment

Refer to protocol Section 4.5 for an overview of participant recruitment, screening, and enrollment processes for this study. Participant recruitment methods may vary across sites, but are expected to rely on active identification and referral of women who perceive themselves to be at heightened risk of HIV acquisition and express interest in learning more about methods to protect themselves.

While recruitment methods may vary across sites, screening and enrollment methods will be standardized across sites, consistent with the requirements of protocol Sections 6.1.1.1 – 6.1.1.2.

4.2.1 Obtaining Informed Consent

Refer to Section 5.0 of this manual for detailed guidance on obtaining informed consent for this study. Written informed consent for maternal and infant study participation must be obtained before any study-specific procedures are performed.

4.2.2 Assigning Participant Identification Numbers

A participant identification (PID) number must be assigned to each potential participant — mother and infant — for whom informed consent for study participation is obtained. The only exception to this requirement applies when a participant has previously been assigned a PID for another IMPAACT or ACTG study. In that case, the previously-assigned PID would be used for IMPAACT 2009. Study site staff should assign PIDs from lists provided by the DMC. Sites may choose (but are not required) to use lists of PIDs that visually link maternal and infant PIDs. Contact the DMC with any questions related to use of PID lists.
4.2.3 Screening for Eligibility

The study eligibility criteria for the PK Component are provided in protocol Sections 4.1 and 4.1.2; procedural eligibility screening requirements are described in protocol Section 6.1.1.1 (PK Component Maternal Screening Visit Group 1 and Group 2) and 6.2.1.2 (PK Component Maternal Enrollment Visit Group 1 and Group 2). Sites are encouraged to perform procedures that are least burdensome and/or most likely to identify ineligibility first. Note that all screening procedures, except for sample collection for HIV RNA, must occur within 30 days prior to entry. A negative HIV test result using Nucleic Acid based testing (e.g. HIV RNA, total nucleic acid, etc.) from a specimen collected within 14 days prior to enrollment is required prior to entry. Multiple visits may be conducted to complete all required screening procedures, if necessary. Sites are encouraged to perform procedures that are least burdensome and/or most likely to identify ineligibility first.

As described in Section 4.2.2, a PID will be assigned to all potential participants for whom informed consent for study participation is obtained. In addition, a study-specific screening number will be obtained for each participant through the DMC’s Subject Enrollment System (SES). Participants who are found to meet all eligibility criteria will be enrolled in the study using the SES.

It is the responsibility of the IoR and other designated study staff to ensure that all required screening procedures are performed and adequately documented, and that only participants who meet the study eligibility criteria are enrolled. Each study site should have an SOP for eligibility determination on file that describes how study staff will fulfill this responsibility; all sites must follow their SOPs when assessing eligibility for all potential participants. *If study staff identify that an ineligible participant has been enrolled, the CMC must be notified as soon as possible* per the communication procedures described in Section 3.0 of this manual.

4.2.4 Screening Failures

Women identified as ineligible for the study should be referred to standard of care HIV prevention services, as needed. If a participant is found to be ineligible, or does not enroll in the study for any reason, the participant will be considered a screen failure. The reason for screen failure should be documented appropriately in the source documentation, and must be entered into the Screening Failure eCRF to record the screening outcome. Study sites should complete and key enter these CRFs as soon as possible after ineligibility is determined so that reasons for non-enrollment can be carefully tracked by the Protocol Team.

4.2.5 Enrolling Eligible Participants

Participants will be considered enrolled in this study upon successful entry of eligibility checklist data into the SES. Refer to protocol Section 6.1.1.2 for Entry Visit requirements, including requirements related to the timing and ordering of Entry Visit procedures, which should be taken into consideration when planning for logistical and staffing needs for these visits.

4.2.6 Screening and Enrollment Logs

Per the DAIDS policy on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials, study sites are required to document screening (including screening failures) and enrollment activity on screening and enrollment logs.
5.0 Informed Consent and Assent

This section contains reference information and guidance for obtaining informed consent in IMPAACT 2009. For the PK Component, this study involves two different informed consent processes:

- **Informed consent for mother and infant study participation:** Written informed consent for mother and infant study participation must be obtained before any study-specific screening or on-study procedures are performed.

  As noted in protocol Section 13.3, and as reflected in the sample informed consent form in protocol Appendix VI, it is expected that maternal participants who have reached the legal age of independent informed consent for research (typically 18 years of age) will provide written informed consent for their own and their infant’s study participation. For maternal participants who have not reached the legal age of independent consent, two options may be considered: 1) parental/legal guardian consent with participant assent or 2) waiver of parental/legal guardian consent. All sites must establish the SOPs that document the locally-applicable legal age of independent informed consent for research, noting whether this age differs for young women who are pregnant. Site SOPs must also specify procedures to be followed when obtaining informed consent and assent for this study, reflecting all applicable IRB/EC determinations and all other IRB/EC requirements.

- **Informed consent for maternal and infant specimen storage and future use:** Informed consent must be requested for storage and future research of maternal and infant specimens that are left over after all protocol-specified testing has been performed. Mothers may choose to either provide or decline informed consent for specimen storage and future use — for themselves and/or for their infants — with no impact on other aspects of their study participation. As indicated on the sample informed consent form for specimen storage and future use in protocol Appendix VIII, this form must be signed or marked regardless of whether informed consent is provided or declined. In addition, specific notations must be recorded on the form to document consent decisions — for mother and infant — for genetic testing.

The remainder of this section provides background information and operational guidance that is applicable to all the informed consent processes noted above.

5.1 General Considerations for Obtaining Informed Consent

Informed consent is a process by which an individual voluntarily expresses his or her willingness to participate in research, after having been informed of all aspects of the research that are relevant to the 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 involving information exchange, comprehension, voluntariness, and documentation. Each of these aspects of the informed consent process is described in greater detail below. Please also refer to Section 4.8 of the International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice (GCP) and the informed consent section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials for further information.

U.S. regulations (45 CFR 46 and 21 CFR 56) specify the elements of informed consent that must be conveyed to consenters through the informed consent process. It is the responsibility of the IoR, and by delegation all study staff involved in conducting the informed consent process, to deliver all required information to consenters.
Based on the reviews completed as part of the IMPAACT 2009 protocol development and study activation processes, there is adequate assurance that once a site-specific study activation notice has been issued, a site’s informed consent forms (ICFs) include all information required by the regulations; however, responsibility for informed consent does not end with preparation of an adequate ICF. It also is the responsibility of the IoR and designated study staff to:

- Deliver all required information in a manner that is understandable to the consenter
- Assure that informed consent is obtained in a setting free of coercion and undue influence
- Confirm that the consenter comprehends the information
- Document the process

Further guidance related to each of these requirements is provided in Sections 5.2-5.5 below. Each site must have on file a study-specific SOP for obtaining informed consent that addresses all aspects of the informed consent process consistent with all applicable regulations, DAIDS policies and procedures, and protocol specifications. All sites must follow their SOPs consistently for all IMPAACT 2009 informed consent processes. All site staff involved in obtaining informed consent must be designated on the study-specific delegation of duties log and listed on the FDA Form 1572 for the study. These staff must be qualified by education, experience, training, and knowledge of the study, as determined by the IoR, and appropriate training documentation must be available to support the IoR’s delegation to these staff.

5.2 Deliver All Required Information in a Manner that is Understandable to the Consenter

The informed consent process should be conducted in the consenter’s preferred language and should reflect whether the consenter is determined to be literate per site SOPs.

If the consenter is literate, begin the informed consent process by providing the consenter with a copy of the ICF to read. Provide the consenter with any other informational materials developed to complement the ICF. If the consenter is not literate, read the materials to her. After the consenter has read the materials (or had them read to her), verbally review the information provided. A checklist or the ICF itself may serve as a useful guide for this. For example, you may note the main points described in each paragraph of the ICF and ask if the consenter has questions or concerns about each point. Listen carefully to the questions and/or concerns expressed by the consenter, and discuss these thoroughly. Take as much time as needed to address each question or concern.

If the consenter is not literate, an impartial witness, literate in the consenter’s preferred language must be present during the entire informed consent process. As part of the documentation steps detailed below, the witness will be asked to sign and date the ICF to attest that the information in the ICF was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter. ICH-E6 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 IMPAACT Operations Center has previously received guidance from the U.S. 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 …” Sites with questions about who may serve as an impartial witness are encouraged to consult with their IRBs/ECs on possible options.

5.3 Assure that Informed Consent is Obtained in a Setting Free of Coercion and Undue Influence

During informed consent discussions, take care to not overstate the possible benefits of the study, nor to underestimate the risks. Describe the alternatives to study participation and emphasize that the availability of medical care and other services routinely obtained from the study site institution will not be affected by the consenter’s decision whether to take part in the study. Encourage the consenter to take as much time as she
needs — and to talk about study participation with others if she chooses — before making a decision.

When a witness is present during the informed consent process, 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 consenter, with emphasis on the fact that the witness is there as a protection for the consenter, not as an agent of the study per se.

5.4 Confirm that the Consenter Comprehends the Information

The consenter must not be asked to agree to take part in the study, or to sign or make her mark on the ICF, until she fully understands the study. Study staff are responsible for ensuring that each consenter understands all aspects of study participation before signing or marking the ICF.

A variety of approaches can be taken to assess comprehension. One approach uses a semi-structured checklist to guide a discussion in which the consenter responds to open-ended questions designed to elicit his/her understanding of key concepts. Other approaches may include documented discussions with the consenter as well as structured knowledge quizzes administered to the consenter.

Regardless of the method used to assess comprehension, if the assessment indicates misunderstanding of aspects of the study, study staff should review those aspects again until the consenter fully understands them. If after additional review and discussion the consenter is not able to demonstrate adequate understanding, she should not be asked to sign or make her mark on the ICF. Similarly, if the consenter has concerns about possible adverse impacts if she were to provide consent, or indicates that she may have difficulty adhering to the study requirements, she should not be asked to sign or mark the ICF unless or until such issues can be resolved to the satisfaction of the consenter and the IoR (or designee).

5.5 Document the Process

U.S. regulations require that informed consent be documented using a written informed consent form approved by the IRB/EC and signed and dated by the consenter or the consenter’s legally authorized representative at the time of consent.

To fulfill this requirement, all signature and date blocks on the ICF should be completed in ink. Legal names should be used. Nicknames or fabricated/falsified names should not be used. Initials may not be used in place of a consenter’s full surname, and it is strongly recommended that initials not be used in place of a consenter’s full first name. However, if a consenter commonly signs his/her name using an initial for his/her first name, the initial may be used, provided this practice is acceptable per the policies of the study site institution(s).

If the consenter is not literate, the witness who was present during the informed consent process must sign and date the ICF to attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter. The consenter’s printed name, signature, and signature date blocks on the ICF should be completed as described in Figure 5-1.

The DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials lists detailed requirements and suggestions for documenting the informed consent process. Study sites must comply with all requirements and are encouraged to comply with all suggestions. To assist with compliance, study staff may use informed consent coversheets similar to the example provided in
Figure 5-2. Sites choosing to use coversheets should identify the coversheets as source documents in their study-specific SOPs for source documentation and should use the coversheets consistently to document each informed consent process conducted with each consenter. All informed consent documentation must be maintained on file in participant study records.

In addition to completing the documentation requirements of the ICF itself, each informed consent process should be documented in a signed and dated chart note. For the main study informed consent process, the note should document that informed consent was obtained before conducting any study procedures. The note also should document adherence to the requirements of the informed consent section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. However, if an informed consent coversheet is used, it is not necessary to transcribe information recorded on the coversheet into the chart note.

Informed consent decisions will also be entered into eCRFs for mothers and infants:

- Informed consent for mother and infant study participation will be entered into the LGW10010, IMPAACT 2009 Informed Consent Status Log eCRF.

- Informed consent for maternal and infant specimen storage and future use will be entered into the TRK10000, Specimen Consent for Non-Protocol Defined Testing eCRF.

Regulations require that consenters be given a signed copy of their ICF. If a consenter opts not to receive a copy, this should be documented and the consenter should be offered an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full ICF.
Figure 5-1
Summary of Considerations for Obtaining Informed Consent from Illiterate Consenters

- Each site must specify procedures for obtaining and documenting informed consent from illiterate persons in its SOP for obtaining informed consent. These procedures must be consistent with the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials and must be followed each time informed consent is obtained from an illiterate consenter. It is recommended that each site seek IRB/EC review and approval of these procedures.

- An impartial witness must be present during the entire informed consent process with an illiterate consenter. The witness must 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 consenter, and that informed consent was freely given by the consenter.

- The site SOP for obtaining informed consent should define who may serve as the witness to the informed consent process.

- Take care to minimize the perception of coercion due to the presence of the witness.

- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process with the consenter should print the consenter’s name below the consenter’s printed name line on the informed consent form, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry (see figure below).

- The consenter should make her mark on the consenter’s signature line.

- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process with the consenter should enter the date upon which the consenter made her mark on the informed consent form below the consenter’s signature date line, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry (see figure below).

- For more information, see Section 4.8 of the ICH GCP guidance and the informed consent section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials.
# Figure 5-2
Sample Informed Consent Coversheet for IMPAACT 2009

<table>
<thead>
<tr>
<th>Field</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother’s identifier</td>
<td></td>
</tr>
<tr>
<td>Infant’s identifier</td>
<td></td>
</tr>
<tr>
<td>Can the mother read?</td>
<td>Yes ☐ ☐ No ⇒ A literate impartial witness should be present during the entire IC process. Record name and role/relationship of witness below.</td>
</tr>
<tr>
<td>Language of IC process</td>
<td>[Language A] ☐ [Language B] ☐</td>
</tr>
<tr>
<td>Version number and version date of informed consent form used during IC process</td>
<td></td>
</tr>
<tr>
<td>Was the father of the child reasonably available during the IC session?</td>
<td>Yes ☐ ☐ No ⇒ Record and explain reason below.</td>
</tr>
<tr>
<td>Start time of IC session</td>
<td>Time:</td>
</tr>
<tr>
<td>Was the IC process conducted per site SOPs and DAIDS policies?</td>
<td>Yes ☐ ☐ No ⇒ Record and explain departures from site SOPs below.</td>
</tr>
<tr>
<td>Was all information required to make an informed decision provided in a language understandable to the mother?</td>
<td>Yes ☐ ☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td>Were all of the mother’s questions answered?</td>
<td>Yes ☐ ☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td>Did the mother comprehend all information required to make an informed decision?</td>
<td>Yes ☐ ☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td>Was the mother given adequate time and opportunity to consider all options, in a setting free of coercion and undue influence, before making an informed decision?</td>
<td>Yes ☐ ☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td>Did the mother choose to provide IC?</td>
<td>Yes ☐ ☐ No ⇒ STOP.</td>
</tr>
<tr>
<td>Date and time at which the mother signed or marked the informed consent form</td>
<td>NA (consent declined, form not signed or marked) Date:</td>
</tr>
<tr>
<td>End time of IC session</td>
<td>Time:</td>
</tr>
<tr>
<td>Did the mother accept a copy of the IC form?</td>
<td>NA (mother chose not to provide informed consent) ☐ Yes ☐ ☐ No ⇒ Offer alternate form of study contact information.</td>
</tr>
<tr>
<td>Notes/Comments (if any)</td>
<td></td>
</tr>
<tr>
<td>Signature of study staff person completing IC process (and this coversheet)</td>
<td></td>
</tr>
</tbody>
</table>
6.0 Study Implementation

Protocol Section 6 and the SoE provide comprehensive information on procedural requirements for conducting study visits. FAQs and other operational tips and reminders related to these protocol specifications will be added to this section as needed.

6.1 Directly Observed Therapy (DOT) Considerations

To be eligible for the PK Component, participants must be willing to initiate and adhere to PrEP and to be observed daily for adherence for 12 weeks. As described in protocol Section 5.1.1.1, study staff must monitor maternal participants’ daily administration of FTC/TDF. Each study site must establish a study-specific SOP describing how this will be accomplished. Further, an individual DOT plan must be developed at study entry for each participant, tailored to her particular circumstances and updated to address any changes in her preference over time. Depending on feasibility, options may include:

1) Directly observed therapy in-person at the study site
2) DOT in-person at the participant’s home or other community-based location (refer to protocol Section 6.1.1 for further detail)
3) Real-time video-based DOT
   a. Live streaming via FaceTime, Tango, Skype, etc.
   b. Time-stamped video recording of subject taking their dose, sent to study staff via text or email. Subject will include relevant dosing information (e.g. time of last meal).

Study staff observing dose, regardless of DOT method, will ensure the tablet has been swallowed by asking the participant to show their mouth is empty after ingestion.

Before using DOT Options 3, participants will be trained on the selected video application(s) and show proficiency in using such applications. Training will include the following key components in addition to video application navigation:

1) If real time video, subject must confirm video connection and that subject can be seen before administering medication.
2) Medication must be clearly visualized in the video/recording before placing in mouth.
3) Video/Recording should not be ended until the dose has been swallowed and subject shows empty mouth
4) Daily dosing window (e.g. before midnight)
5) How and where to send time-stamped videos (e.g. as soon as service is available, to study email and/or phone)

In the rare event that one of the three options listed above cannot be used, study staff should contact participants to self-report their daily dose administration via telephone call, audio message, text message, and/or still photo.

Study staff will document the nature of observation for each dose taken on tracking form TRK10005 (IMPAACT 2009 Directly-Observed Therapy Tracking Log). Self-reported administration and missed doses will also be documented on this form.
Note: PK Component participants are only considered evaluable for data analysis if they swallow adequate PrEP doses and are directly observed doing so and suitable documentation is available in the study chart (see protocol Section 9.1.1). It is important for sites to frequently review DOT performance for individual participants and their site overall to institute remedial measures in good time.

6.2 Integrated Next Step Counseling (iNSC)

A guide to Integrated Next Step Counseling (iNSC) will be posted on the IMPAACT 2009 study webpage. For questions or clarifications on any material, please query the IMPAACT 2009 protocol team at impaact.team2009@fstrf.org.

6.3 Administering Study-Specific Questionnaires

During the PK Component, two study-specific questionnaires will be administered to enrolled mothers:

- QLW10046: Sociodemographics Questionnaire
- QLW10055: Risk and Sexual Behavior Questionnaire

Each questionnaire will be interviewer-administered using either the paper-based forms (source documents), then entered into the eCRFs OR directly entered into the into the eCRFs. See MOP Section 6.4.5 for instructions on recording “other” responses that require translation. To standardize this interviewer-administered data collection from site to site, and to maximize data quality, questionnaires must be administered in a non-biased, non-judgmental manner. Study staff should help participants feel comfortable sharing their personal information and opinions while asking questions in a consistent manner from participant to participant.

Study-specific questionnaires must be administered in the preferred language of each participant. If the study staff member administering the questionnaire is not fluent in the participant’s preferred language, a translator (third party) may be used to translate questions and responses in real time; however, every effort should be made to have a staff member who is fluent in the participant’s preferred language administer the questionnaire. As a condition for site-specific study activation, each site will be required to translate the questionnaires into all applicable local languages and to submit their translations and back-translations (into English) for review and approval by the Protocol Data Managers. Sites should follow local regulations for obtaining IRB approval of questionnaires. Please contact the Data Managers with any questions related to this process.

For questionnaires with “other specify” response options, participant responses should be recorded word-for-word in the language in which the response was given. After the questionnaire is completed, the response should be translated into English, for entry into eCRF screens. It is generally expected that the study staff member who administered the questionnaire will perform this translation; other study staff members are also permitted to perform this translation, provided they are fluent in both English and the language in which the response was given.

The remainder of this section provides general guidance for administering all interviewer-administered questionnaires.

6.3.1 General Guidance for Questionnaire Administration

An interviewer uses both verbal and non-verbal techniques to obtain the most honest, accurate, and thorough responses from participants. These techniques are discussed below.
6.3.2 Welcoming the Participant

When a participant decides to take part in a study, everything about the study is new. Help make her feel comfortable.

- Considering offering the participant a cup of tea or other refreshment.

- Introduce yourself and try to create rapport (connection) between yourself and the participant to help her feel comfortable during administration of the questionnaire.

- Speak with the participant and administer questionnaires in the participant’s preferred language. Choose the local language questionnaire that corresponds to the participant’s preferred language and read directly from that form. Do not use another language form and translate in real-time.

- If considered helpful, offer the participant a blank copy of the form (in the preferred language) to read along as the questionnaire is administered. It is also acceptable for the participant to see the copy of the questionnaire being completed by the interviewer, as responses are being recorded, because this can reduce anxiety and increase collaboration.

- Some questionnaires include introductory statements to help prepare the participant for sensitive questions. Read these introductions as they appear on the forms.

6.3.3 Asking Sensitive Questions

This study addresses sensitive issues: employment status, income level, HIV risk perception, sexual behavior, and others. Your level of comfort with asking sensitive questions will affect the participant's comfort and answers to the questions. If you ask the questions in a confident and supportive manner, the participant will feel more confident and comfortable answering the questions. Make eye contact with the participant to let her know that you are listening to her and aware that she is being asked difficult questions. Avoid apologizing for questions or making facial gestures that might show you feel any way but neutral about a question or the participant's response. If the participant feels judged, she will be less likely to share honestly with you.

6.3.4 Reading Items Aloud

Read all items to the participant word-for-word and speak clearly. Avoid re-phrasing questions because this can change the meaning of the question, making it inconsistent with questions administered to other participants. Provide explanation or interpretation if necessary only after reading the item word-for-word. Avoid tangential—though related—counseling and educational discussions during data collection. When applicable, acknowledge questions and concerns raised by the participant during the questionnaire and state that these can be discussed after the questionnaire is completed.

Read the questions with interest and variability, so you do not sound automated. Emphasize the important words in a question, so that the meaning of the question comes through.

For questions with multiple sub-parts, read all sub-parts to the participant and mark the appropriate response for each, based on the participant’s answers.
6.3.5 Recording Participant Responses Verbatim

Often, questions will have a list of response categories to capture the participant’s response. Sometimes, an “other, specify” option is included for responses that do not fit into one of the categories already listed. When “other, specify” must be used, record the participant’s verbatim response, word-for-word, in the language spoken by the participant. Once the questionnaire is completed, go back and translate the local language text into English, for entry into eCRF screens. **Do not** translate in real-time during administration of the questionnaire, even if doing direct data entry.

6.3.6 Watching for Non-Verbal Cues

A participant may give you one answer verbally, but express something else using body language or facial expressions. Although you should not question a participant so as to make her feel like you don't trust her answers, be aware of whether she is giving you non-verbal cues that indicate she is not feeling comfortable, not taking the questionnaire seriously, or not answering honestly.

6.3.7 Checking Your Work

While administering a questionnaire, follow any written form instructions and guidance. Also, make sure the participant is understanding and responding to you, and that you record all reported information on the questionnaire form.

After the questionnaire is completed, and while the participant is still at the study site, review the questionnaire form for accuracy and completeness. This review step is not intended as an active review with the participant to confirm all of her responses; rather, it is a check to help ensure that any items that might have accidentally been missed or mis-marked can be completed or corrected before the participant leaves the study site. Thereafter, questionnaire forms may undergo additional reviews, following site SOPs for QC/QA.

7.0 Expedited Adverse Event Reporting Requirments

Refer to protocol Section 7.3 for detailed information on expedited adverse event (EAE) reporting requirements for this study. Other important references and resources related to EAE reporting include:

- Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0)
- DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, dated July 2017
- Package Insert for Emtricitabine/tenofovir disoproxil fumarate (Truvada) package insert
- DAERS Site User Instructional Guide for EAE Reporting
- DAERS Reference Guide for Site Reporters and Study Physicians
- DAIDS safety training resources

The DAERS and DAIDS resources listed above are available at:

https://rsc.tech-res.com/clinical-research-sites/safety-reporting/daers
https://rsc.tech-res.com/clinical-research-sites/safety-reporting/safety-training-resources

Note that even when EAE reporting is not required, all maternal and infant adverse events must be source documented and selected adverse events must be entered into eCRFs, per protocol Section 7.2.