IMPAACT 2001

A Phase I/II Trial of the Pharmacokinetics, Tolerability, and Safety of Once-Weekly Rifapentine and Isoniazid in HIV-1-infected and HIV-1-uninfected Pregnant and Postpartum Women with Latent Tuberculosis Infection

Manual of Procedures

Version 1.1
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IMPAACT 2001 Manual of Procedures

Section	Comments
Section 1 Study Overview	• First implementation version
Section 2 Preparing for the Study	• First implementation version
Section 3 Study-Related Information and Communications	• First implementation version
Section 4 Participant Accrual	• First implementation version
Section 5 Recruitment, Screening, and Enrollment	• First implementation version
Section 6 Follow-Up Visits and Procedures	• First implementation version
Section 7 Anthropometric Measurements for Women	• First implementation version
Section 8 WHO TB Symptom Screen and TST	• First implementation version
Section 9 Specimen Collection and Laboratory Considerations	• First implementation version
Section 10 Expedited Adverse Event Reporting to DAIDS	• First implementation version

Table of Contents

1.0 Study Overview

IMPAACT 2001 is a Phase I/II, multicenter, open label, study of the pharmacokinetics (PK) and safety of rifapentine (RPT) and isoniazid (INH) in pregnant and postpartum women with latent tuberculosis (TB). The aim of the study is to determine the optimal dose of RPT in the second and third trimesters of pregnancy and postpartum.

The study involves two cohorts of HIV-1-infected and HIV-1-uninfected pregnant women based on gestational age at enrollment:

Cohort 1: Second Trimester
Women enrolled during their second trimester (≥14 to <28 weeks) and provided RPT and INH with pyridoxine for 12 weeks (n=25 evaluable)

Cohort 2: Third Trimester
Women enrolled during their third trimester (≥28 to ≤34 weeks) and provided RPT and INH with pyridoxine for 12 weeks (n=25 evaluable)

Approximately 82 pregnant women and their infants are expected to be enrolled into the study to achieve 50 mothers (25 per cohort) who are evaluable for PK analyses. Within each cohort, enrollment of at least 10 evaluable HIV-1-infected women will be targeted.

All women will receive 12 directly observed once-weekly doses of RPT (900mg) and INH (900mg) taken with pyridoxine (25 to 100mg). Depending on the timing of enrollment and the timing of delivery, the number of weekly doses provided during pregnancy versus postpartum will vary across women. Women will be followed through 24 weeks postpartum, and infants will be followed for 24 weeks from birth. Intensive PK evaluations will be performed at the Entry visit, and sparse PK evaluations will be performed at the last weekly visit (Week 11 visit). After the weekly visits are completed, monthly visits will be conducted; following delivery, monthly visits will also be conducted for infants. Participant safety, as well as immunologic and virologic outcomes, will be monitored throughout the course of follow-up for both mothers and infants.

2.0 Preparing for the Study

This study will be conducted at the following IMPAACT clinical research sites (CRSs), which were selected by the Protocol Team based on review and approval of a Site Application and Site Implementation Plan (SIP):

CRS 5114	Bronx Lebanon Hospital Family Research Center CRS, New York, United States
CRS 5115	Siriraj Hospital Mahidol University CRS, Bangkok, Thailand
CRS 5121	Kenya Medical Research Institute Walter Reed Project CRS, Kericho, Kenya
CRS 12001	University of North Carolina Project Lilongwe CRS, Lilongwe, Malawi
CRS 30022	Les Centres GHESKIO CRS, Port-au-Prince, Haiti
CRS 31890	Harare Family Care CRS, Harare, Zimbabwe

A copy of the approved Site Application and SIP should be maintained in each site's study-specific essential document files.

2.1 Investigator Responsibilities

At each site, this study must be conducted in accordance with the United States (US) 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 website and must be followed throughout implementation of IMPAACT 2001:

https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

This study also must be conducted in accordance with 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 of the above-listed regulations, policies, and guidelines should be maintained in on-site essential document files.

The Investigator of Record (IoR) at each site must sign a US Food and Drug Administration (FDA) 1572 Form 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 this form 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

IoRs may delegate their obligations and responsibilities for conducting this study 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 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, 21 CFR 56 and the ICH GCP guidance, as well as on the website of the US 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 2001 involves maternal and pediatric participants, IRBs/ECs must consider the potential benefits, risks, and discomforts of the study to maternal, fetal, and infant participants and assess the justification for their inclusion in the study (see protocol Section 13.2). As part of this assessment, IRB/ECs must assess the level of risk to participants 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 sites with SIPs and Site Applications approved by the Protocol Team are permitted to submit for protocol registration for the study. After all required DRA and IRB/EC approvals are obtained, site staff are then responsible for submitting documentation of the approvals and other required documentation to the PRO.

Further information on the protocol registration process can be found in the *DAIDS Protocol Registration Manual*. Upon confirming receipt of all required documentation, the PRO will issue a 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. ***For this study, sites must obtain a registration notification for protocol Version 1.0 and Letter of Amendment (LoA) #1 and #2 prior to study initiation.***

2.3 Site-Specific Study Activation

Prior to conducting any study procedures, each site must obtain all required approvals as described in Section 2.2 above. Each site must also complete study-specific activation requirements specified by the Protocol Team to obtain approval to begin study implementation. These requirements are listed on the IMPAACT 2001 Site-Specific Study Activation Checklist, which is available from the IMPAACT Operations Center.

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-Related Information and Communications

All IMPAACT 2001 visits and procedures must be conducted in accordance with the study protocol. The purpose of this manual is to supplement the protocol, not to replace or substitute for it. In the event that this manual is inconsistent with the protocol, the specifications of the protocol take precedence. Please notify the IMPAACT Operations Center of any such inconsistencies.

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

- ***General questions:*** Questions related to protocol interpretation or study implementation, including administrative, ethical, regulatory, counseling, data, and laboratory operations should be emailed to the IMPAACT 2001 Protocol Team as listed in Figure 3-1. Any questions that are not answered by the protocol or this document should also be emailed to the IMPAACT 2001 Protocol Team.

- ***Clinical and toxicity management questions and notifications:*** Questions concerning clinical management of study participants and adverse experiences should be emailed to the IMPAACT 2001 Core Team as listed in Figure 3-1. Additional detail is listed in Figure 3-2.

- ***Study implementation questions***: Questions related to participant eligibility, co-enrollment, potential enrollment of an ineligible participant, and/or deviation from other protocol requirements for screening and enrollment should also be directed to the IMPAACT 2001 Core Team as listed in Figure 3-1.

- ***Other types of questions*** should be managed as listed in Figure 3-1.

Figure 3-1
IMPAACT 2001 Study-Related Communications

Topic	Contact
Adding site staff to protocol email group **(IMPAACT.prot2001@fstrf.org)**	**User Support** **user.support@fstrf.org** *(include the protocol number in the subject line of your email message)*
Any aspect of protocol interpretation or study implementation not listed below	**IMPAACT 2001 Protocol Team** **impaact.team2001@fstrf.org** *for triage to other team members as needed*
Clinical management issues	**IMPAACT 2001 Core Team** **impaact.core2001@fstrf.org**
Participant eligibility, potential enrollment of an ineligible participant, and/or deviation from protocol requirements for eligibility determination and/or enrollment	**IMPAACT 2001 Core Team** **impaact.core2001@fstrf.org**
Co-enrollment	**IMPAACT 2001 Core Team** **impaact.core2001@fstrf.org**
Data management computer and screen problems	**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 drugs (other than study drug orders)	**Protocol Pharmacist** **oladapo.alli@nih.gov** *or by phone: +240-627-3593*
Study drug orders	**Clinical Research Products Management Center** **BIO.CRPMC.Ph@Thermofisher.com** *(or by phone: +301-294-0741)*
Expedited Adverse Event (EAE) Reporting	**DAIDS RSC Safety Office** **DAIDSRSCSafetyOffice@tech-res.com** *or by phone: 800-537-9979 or +301-897-7448* *or by fax: 800-275-7619*
DAIDS Adverse Experience Reporting System (DAERS)	**NIAID CRMS Support** **CRMSSupport@niaid.nih.gov** *(questions also may be submitted from within the DAERS application)*

When submitting clinical management questions to the IMPAACT 2001 Core Team, to help ensure that Core Team members have adequate information to respond in a timely manner, please address each of the points listed in Figure 3-2.

Figure 3-2
IMPAACT 2001 Core Team Clinical Management Communications

Questions for IMPAACT 2001 Core Team: Please copy and paste this listing into the body of your email message to impaact.core2001@fstrf.org to help ensure that all required information is included. Include the protocol number and PID in the subject line of your email.

1. Site name and number:
2. Name of person submitting query:
3. Participant type:
   - Mother
   - Infant
   - Both mother and infant
4. PID(s):
5. Reason for query (choose one):
   a. Consultation on eligibility or enrollment (describe in case description)
   b. Consultation on AE or toxicity management (specify severity grade in case description)
   c. Consultation on study drug (RPT+INH) management (describe in case description)
   d. Other (specify in case description)
6. Cohort: 1 or 2
7. Age of participant:
8. Current week on study:
9. Current week of study drug (RPT+INH) dosing (include number of doses received and drug names and doses of ARVs, if applicable):
10. Case description and question or notification for Core Team:

Print and file a copy of the email exchange in the participant's study chart.

3.1 Case Report Form (CRF) Completion and Data Entry

The Data Management Center (DMC) has developed a Forms Manual to assist site staff in the accurate completion of CRFs used for DAIDS-sponsored Clinical Trials. The Forms Manual is located in the DMC IMPAACT Portal under the Case Report Forms heading.

The manual outlines standards and guidelines which when followed, will result in fewer queries, shorter delinquency lists, and most important, straightforward and timely analyses. The manual includes sections that cover topics such as the CRF notebook, reporting data, understanding forms, forms components and conventions, submitting data, data collection formats and participant status categories.

For reporting TB diagnosis, sites should refer to CRF Appendix 100 for the TB diagnosis definitions. For all other diagnoses, CRF Appendix 100 (or the most current version of the CRF appendix) should be used. Conditions listed on the "Do Not Report" list do not need to be recorded on CRFs. To obtain the most current version of the CRF appendix, please refer to the IMPAACT Portal of the DMC website:

https://www.frontierscience.org/

4.0 Participant Accrual

The study involves two cohorts of HIV-1-infected and HIV-1-uninfected pregnant women based on gestational age:

Cohort 1: Second Trimester
Women enrolled during their second trimester (≥14 to <28 weeks) and provided RPT and INH with pyridoxine for 12 weeks (n=25 evaluable)

Cohort 2: Third Trimester
Women enrolled during their third trimester (≥28 to ≤34 weeks) and provided RPT and INH with pyridoxine for 12 weeks (n=25 evaluable)

Approximately 82 pregnant women and their infants are expected to be enrolled into the study to achieve 50 women (25 per cohort) who are evaluable for PK analyses. Within each cohort, enrollment of at least 10 evaluable HIV-1-infected women will be targeted. Women will be considered evaluable if they meet any of the following criteria:

- Contribute any data to the Intensive PK or Sparse PK sampling collections
- Complete the study drug regimen (Per Section 5.1.2 of the protocol, women will be considered to have completed the study drug regimen if they receive at least 11 doses of RPT+INH+pyridoxine within a 16-week window. However, 12 weeks in a row is ideal).

Accrual is expected to be completed within 12 months, beginning on the date of the first participant enrollment across sites. Each study site should have a standard operating procedure (SOP) for participant accrual on file. 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.

Study sites may enroll participants in Cohort 1, Cohort 2, or both. 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 DMC will report the number of women screened and the number of mother-infant pairs enrolled in each cohort by HIV infection status and their infants to the Protocol Team at least monthly.

Throughout the accrual period, the Protocol Team will review accrual and other performance data from each site to determine whether accrual targets should be adjusted across sites to achieve the study objectives most efficiently and to determine when to discontinue accrual at each site. 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.

5.0 Recruitment, Screening, and Enrollment

At each site, recruitment of potential study participants may begin after a site-specific study activation notice has been issued. Potential participants are expected to be identified in antenatal care clinics. For both cohorts, when a potentially eligible participant is identified, she will be informed about the study and asked to provide written informed consent for herself and her infant for the study. Study-specific procedures may not be performed before written informed consent is obtained.

5.1 Informed Consent

This section contains information and guidance for obtaining informed consent for IMPAACT 2001.

Informed consent is a process by which an individual voluntarily expresses her willingness to participate in research, and her willingness to allow her infant 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 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.

US 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 of all study staff involved in the informed consent process, to deliver all required information to consenters.

Based on the reviews completed as part of the IMPAACT 2001 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 5.1.1-5.1.3 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 2001 informed consent processes.

5.1.1 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. It is important that 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.

If the consenter is literate, begin the informed consent process by providing the consenter with a copy of the ICF to read. Also provide her 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, site staff 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 literate witness 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 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 …" Sites with questions about who may serve as an impartial witness are encouraged to consult with their IRBs/ECs on possible options.

Please see Appendix I for a summary of considerations for obtaining informed consent from illiterate consenters.

5.1.2 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 understate the risks. Also 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 or not 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.

5.1.3 Document the Process

US regulations require that informed consent be documented through the use of 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. 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 her name using an initial for 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.

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 examples provided in Appendix II. 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. 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 or otherwise duplicate information recorded on the coversheet into the chart note.

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.

5.2 Screening and Enrollment Procedures

After written informed consent is obtained, study sites should obtain a screening number by completing the PS2001 IMPAACT Screening Checklist in the Subject Enrollment System (SES) on the DMC Portal. Study sites can then assign PIDs to the mother and infant and proceed with the procedures listed in Figure 5-1 to provide information relevant to eligibility determination for the study. There is no specified ordering or required sequence for these procedures; however, study sites are encouraged to perform procedures that are least burdensome and/or most likely to identify ineligibility first. Screening evaluations may be performed on multiple days and, per protocol Section 6.1, may be discontinued once ineligibility is determined. Women identified as ineligible for the study should be referred to non-study care and treatment as needed. A Screening Failure and Non-Enrollment Results (SCR0053) CRF must be completed for each woman who provides informed consent but does not enroll in the study for any reason. 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.

For women identified as potentially eligible at their screening visits, a study entry visit will be scheduled pending receipt of screening laboratory test results. The procedures listed in Figure 5-2 should be

performed at the entry visit. Mother-infant pairs whose eligibility is confirmed should then be enrolled in the study using the SES. Following successful completion of the enrollment process, study drug may be prescribed and dispensed and all other entry visit procedures may be performed.

It is the responsibility of the IoR and other designated study staff to ensure that all required screening evaluations are performed and adequately documented, and that only women 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. Any questions related to eligibility should be emailed to the IMPAACT 2001 Core Team. The Core Team should also be notified in the event that study staff identify that an ineligible participant has been enrolled, per the communication procedures described in Section 3.0 of this manual.

Figure 5-1
IMPAACT 2001 Screening Visit Procedures

SCREENING VISIT PROCEDURES
Within 2 weeks prior to study entry

- Perform procedures specified in Section 6.1 of the protocol
- Obtain participant written informed consent *(must precede any study-specific procedures)*
- Obtain screening number from the SES
- Assign PIDs to the mother and infant
- Review available medical records and collect medical and medications history information including:
  - Age
  - Documentation of HIV-1 infection status (*applies to both HIV-1-infected and HIV-1-uninfected potential participants)*
  - Complete TB history, symptoms, risk, and exposure
  - TST or IGRA (perform if needed and not available in medical record for *HIV-1-infected only* potential participants per inclusion criterion 4.1.3)
  - Complete ART medication history, if applicable
  - For HIV-1-infected potential participants, documentation of current prescription of EFV + 2 NRTI regimen and reports taking or planning to take the regimen for at least 2 weeks prior to enrollment
  - Other history relevant to the study inclusion and exclusion criteria
- Perform complete physical exam including:
  - Temperature, pulse, blood pressure, and respirations
  - Weight and mid-upper arm circumference
  - Assess general appearance, cardiac exam, pulmonary exam, lymph node exam, and abdominal exam
- Perform obstetrical exam including
  - Assess gestational age, presence of severe fetal abnormalities and multiple births by ultrasound
  - Assess fetal movement reported by the mother and fetal heart sounds on Doppler
- Perform WHO TB symptom screen (see Section 8.1), and Gene Xpert, shielded chest x-ray, or sputum microscopy to confirm evidence of probable or confirmed active TB, for purposes of eligibility determination per exclusion criterion 4.2.1
- Assess eligibility thus far based on all available information:
  - ⇒ If potentially eligible, schedule Entry visit; provide reminders prior to the Entry visit, including instruction to refrain from eating 2 hours (except water) before the PK sampling dose of study drug.
  - ⇒ If not potentially eligible, discontinue study procedures but complete documentation as listed below
- Document visit per site SOPs and DAIDS policies for source documentation
- Update screening and enrollment log
- Complete and submit required CRFs. If participant is found to be ineligible, or does not enroll for any reason, each site must also complete a Screening Failure and Non-Enrollment Results CRF (SCR0053)

Figure 5-2
IMPAACT 2001 Entry Visit Procedures

ENTRY VISIT PROCEDURES
(Day 0 and 72 hours following)

- Perform procedures specified in Section 6.2 of the protocol
- Review available medical records, screening laboratory test results, and findings of all other screening evaluations to determine whether participant remains potentially eligible
  - ⇒ If eligible, continue
  - ⇒ If not eligible, discontinue study procedures but complete documentation as listed below
- Prior to enrollment:
  - Review informed consent and confirm woman's continued consent for study participation
  - Assess TB symptoms, risk and exposure
  - Update medical and medications history
  - Perform targeted physical exam including:
    - Temperature, pulse, blood pressure, and respirations
    - Height and weight
    - Other evaluations considered clinically appropriate or indicated by examining clinician
  - Record baseline adverse events (AEs)
  - Assess fetal movement reported by the mother and heart sounds on Doppler
  - Complete final eligibility determination and confirmation
  - Complete paper-based eligibility checklist
- Review, confirm, and document eligibility per site SOPs:
  - ⇒ If eligible, continue
  - ⇒ If not eligible, discontinue study procedures but complete documentation as listed below
- On the day of enrollment:
  - Enter checklist data into the SES to enroll the mother-infant pair, print and file a copy of the confirmation file.
  - Ideally in the morning, administer directly observed therapy (DOT) of the study drug regimen (RPT, INH, and pyridoxine) *within 30 minutes of the meal provided*.
    - The type of meal (e.g. high in fat), quantity (full meal or light snack), and time of food intake should be recorded on the Maternal Pharmacokinetics CRF (PKW0392).
    - Participants should withhold from further intake of food or drink (except water) until 3 – 4 hours after administration of the study drug dose.
  - Provide any available test or laboratory results
- Schedule Week 1 visit; provide reminders for Week 1 visit and site contact instructions
- Document visit per site SOPs and DAIDS policies for source documentation
- Update screening and enrollment log
- Complete and submit required CRFs
- If a participant is determined to be ineligible, or does not enroll for any reason, each site must also complete a Screening Failure and Non-Enrollment Results CRF (SCR0053).

6.0 Follow-Up Visits and Procedures

6.1 Follow-up Visit Schedule

Women enrolled in this study will be scheduled to complete 11 weekly follow-up visits, followed by monthly visits until 24 weeks postpartum. Women who complete the study drug regimen prior to delivery will also have a visit during the immediate postpartum period (within 3 days of delivery). Infants enrolled into the study will be scheduled for monthly follow-up visits until 24 weeks of life. Figure 6-1 provides an illustration of the study visit schedule for a sample pair in which the woman enrolls in the study on 1 December 2016 at 14 weeks gestation and delivers her infant at 40 weeks gestation. Visits highlighted in yellow involve required PK evaluations.

Figure 6-1
Follow-up Visit Schedule
for a Sample Pair in which the Woman Enrolls in IMPAACT 2001 on 1 December 2016 at 14 weeks gestation (Cohort I)

MATERNAL VISITS				INFANT VISITS		
Maternal Visits per SoE	Gestational Age/Weeks Postpartum on Target Date	Maternal Target Date	Maternal Visit Window	Infant Visits per SoE	Infant Target Date	Infant Visit Window
Entry	14 Weeks	1 DEC 2016				
Week 1	15 Weeks	8 DEC 2016	6 DEC – 10 DEC			
Week 2	16 Weeks	15 DEC 2016	13 DEC – 17 DEC			
Week 3	17 Weeks	22 DEC 2016	20 DEC – 24 DEC			
Week 4	18 Weeks	29 DEC 2016	27 DEC – 31 DEC			
Week 5	19 Weeks	5 JAN 2017	3 JAN – 7 JAN			
Week 6	20 Weeks	12 JAN 2017	10 JAN – 14 JAN			
Week 7	21 Weeks	19 JAN 2017	17 JAN – 21 JAN			
Week 8	22 Weeks	26 JAN 2017	24 JAN – 28 JAN			
Week 9	23 Weeks	2 FEB 2017	31 JAN – 4 FEB			
Week 10	24 Weeks	9 FEB 2017	7 FEB – 11 FEB			
Week 11	25 Weeks	16 FEB 2017	14 FEB – 18 FEB			
Maternal Weekly Visits End – Monthly Visits Begin						
Week 15	29 Weeks	16 MAR 2017	2 MAR – 30 MAR			
Week 19	33 Weeks	13 APR 2017	30 MAR – 27 APR			
Week 23	37 Weeks	11 MAY 2017	27 APR – 25 MAY			
Assume Delivery at 40 weeks on 1 June 2017						
Week 26	0-3 Days PP	1 JUN 2017	1 JUN – 4 JUN	Newborn visit	1 JUN 2017	1 JUN – 4 JUN
Week 30	4 Weeks PP	29 JUN 2017	15 JUN – 13 JUL	Week 4	29 JUN 2017	15 JUN – 13 JUL
Week 34	8 Weeks PP	27 JUL 2017	13 JUL – 10 AUG	Week 8	27 JUL 2017	13 JUL – 10 AUG
Week 38	12 Weeks PP	24 AUG 2017	10 AUG – 7 SEP	Week 12	24 AUG 2017	10 AUG – 7 SEP
Week 42	16 Weeks PP	21 SEP 2017	7 SEP – 5 OCT	Week 16	21 SEP 2017	7 SEP – 5 OCT
Week 46	20 Weeks PP	19 OCT 2017	5 OCT – 2 NOV	Week 20	19 OCT 2017	5 OCT – 2 NOV
Week 50	24 Weeks PP	16 NOV 2017	2 NOV – 30 NOV	Week 24	16 NOV 2017	2 NOV – 30 NOV

Figure 6-2 provides an illustration of the study visit schedule for a sample pair in which the woman enrolls on 1 December 2016 at 34 weeks gestation and delivers at 40 weeks gestation. Visits highlighted in yellow involve required PK evaluations; visits highlighted in green involve plasma collection and breast milk PK evaluations for eligible participants; and visits highlighted in blue indicate potential weekly visits for the single coagulation profile collection for participants that are ≥ 34 weeks gestational age only and taking the study drug regimen.

Figure 6-2
Follow-up Visit Schedule
for a Sample Pair in which the Woman Enrolls in IMPAACT 2001 on 1 December 2016 at 34 weeks gestation (Cohort II)

MATERNAL VISITS				INFANT VISITS		
Maternal Visits per SoE	**Gestational Age/Weeks Postpartum**	**Maternal Target Date**	**Maternal Visit Window**	**Infant Visits per SoE**	**Infant Target Date**	**Infant Visit Window**
Entry	34 weeks	1 DEC 2016				
Week 1	35 weeks	8 DEC 2016	6 DEC – 10 DEC			
Week 2	36 weeks	15 DEC 2016	13 DEC – 17 DEC			
Week 3	37 weeks	22 DEC 2016	20 DEC – 24 DEC			
Week 4	38 weeks	29 DEC 2016	27 DEC – 31 DEC			
Week 5	39 weeks	5 JAN 2017	3 JAN – 7 JAN			
Assume Delivery at 40 weeks on 12 January 2017						
Week 6	40 weeks	12 JAN 2017	10 JAN – 14 JAN	Newborn visit	12 JAN 2017	10 JAN – 14 JAN
Week 7	1 Week PP	19 JAN 2017	17 JAN – 21 JAN			
Week 8	2 Week PP	26 JAN 2017	24 JAN – 28 JAN	Week 4	9 FEB 2017	26 JAN – 23 FEB
Week 9	3 Week PP	2 FEB 2017	31 JAN – 4 FEB			
Week 10	4 Week PP	9 FEB 2017	7 FEB – 11 FEB			
Week 11	5 Week PP	16 FEB 2017	14 FEB – 18 FEB			
Maternal Weekly Visits End – Monthly Visits Begin						
Week 15	9 weeks PP	16 MAR 2017	2 MAR – 30 MAR	Week 8	9 MAR 2017	23 FEB – 23 MAR
Week 19	13 weeks PP	13 APR 2017	30 MAR – 27 APR	Week 12	6 APR 2017	23 MAR – 20 APR
Week 23	17 weeks PP	11 MAY 2017	27 APR – 25 MAY	Week 16	4 MAY 2017	20 APR – 18 MAY
Week 27	21 weeks PP	8 JUN 2017	25 MAY – 22 JUN	Week 20	1 JUN 2017	18 MAY – 15 JUN
Week 31	25 weeks PP	6 JUL 2017	22 JUN – 20 JUL	Week 24	29 JUN 2017	15 JUN – 13 JUL

Further key points regarding the follow-up visit schedule are as follows:

- Maternal target visit dates are counted from the day of study entry; day of entry = Day 0. Infant target visit dates are counted from the day of birth; day of birth = Day 0.

- Each visit should ideally be conducted on the target date, but may be conducted on any day within the allowable visit window. Maternal and infant visits should be scheduled on the same day, whenever possible, as shown by the allowable maternal and infant visit windows in Figure 6-2.

- Sites should establish SOPs to be notified when a participant is admitted for delivery, and provide any relevant information or reminders to mothers approaching labor and delivery.

6.2 Follow-up Visit Procedures for Women on Study Drug

A listing of follow-up visit procedures for women on study drug is provided in protocol Section 6.3. Unless otherwise specified, all procedures should be performed at all visits. There is no specified ordering or required sequence for most procedures at most visits. However, further operational instructions are provided below.

- Women will be asked to withhold food and drink (except water) until 3 – 4 hours after the study drug dose has been administered for each PK sampling dose.

- Women will be instructed to withhold food at least 2 hours *prior* to the beginning of each PK sampling dose of the study drug regimen (Entry, weekly visit of last dose of study drug, and if eligible for breast milk PK collections first and second weeks postpartum).

  Note: This does *not* include the meal taken within 30 minutes at the site before each administration of the study drug regimen.

- Women who are taking the study drug regimen and ≥ 34 gestational age should have 5mL of blood collected for a coagulation profile at one weekly visit prior to completion of the study drug regimen. See Figure 6-2 for an example of potential weekly visits highlighted in blue to perform this collection for a woman who enrolls at 34 weeks gestation.

- During weekly visits, women should have blood collected for complete blood count (CBC) and liver function tests **every 4 weeks**.

- The Sparse PK visit (conducted on the visit of the woman's last dose of the study drug regimen) should ideally be initiated in the morning.

- Women who are taking study drug following delivery, and breastfeeding, will also have breast milk PK and plasma samples collected at the following time points:

First Weekly Visit After Delivery	Second Weekly Visit After Delivery	Last Study Drug Dose Visit
Collect breast milk and plasma **3-4 hours** after the study drug dose	Collect breast milk and plasma **6 hours** after the study drug dose	Collect breast milk *only* **24 hours** after the study drug dose

Given all of the above, each site should establish SOPs for providing all relevant information and reminders to participants to optimize compliance with protocol requirements. As a reminder, the food type, quantity, and time the meal is given prior to each PK sampling dose should be recorded on CRFs (PKW0392 and PKW0394).

At each follow-up visit, study clinicians must assess whether any additional evaluations are clinically indicated. Refer to protocol Section 8.1 for detailed guidelines on management of adverse events (AEs).

6.3 Infant Follow-up Visit Procedures

A listing of follow-up visit procedures for infants is provided in protocol Sections 6.5 and 6.6. Unless otherwise specified, all procedures should be performed at all visits. There is no specified ordering or required sequence for most procedures at most visits. However:

- Infants born to mothers on study drug at delivery may be eligible for the intensive PK sampling at the Newborn visit. Infants that meet the criteria for the PK collection per Section 10.2.4 of the protocol will need to have the blood drawn for the PK sampling within 72 hours of the mother's most recent study drug dose.

- Infants born to mothers who have received study drug within 72 hours *prior to delivery* are eligible to participate in the cord blood sample collection at sites with the capacity to complete this collection.

7.0 Anthropometric Measurements for Women

7.1 General Instructions

Whenever possible, measurements should be taken by a team of two measurers. One measurer takes the measurements while the other measurer records. The measurer taking the measurements calls out the results to the recorder. The recorder repeats the results and then calls out the name of the next measurement. The measurer keeps the measuring instrument in place until the recorder repeats the number. The recorder checks the participant's position during the procedure. The participant's cooperation is extremely important for obtaining accurate measurements.

Circumference measurements are made once before repeating them a second time in the same sequence by the same observer. Document measurement conditions (type of equipment use, participant's behavior during procedure, etc.). Always take two measurements. A third measurement will be needed when the second measurement differs from the first by more than 0.5 cm.

All measurements should be taken on the right side of the participant being measured. If measurement on the right side is contraindicated or otherwise not possible, the measurement should be taken on the left side and the reason for this should be recorded in source documents and on relevant case report forms. If a participant's first measurement is taken on the left side, for consistency, all subsequent measurements should also be taken on the left side.

7.2 Mid-Upper Arm Circumference (MUAC) Measurements

7.2.1 General Instructions

Equipment: Fiberglass or paper measuring tapes specific to 1.0 mm
Grease marking pencil or washable felt-tip marker

In IMPAACT 2001, MUAC will be measured in women only at screening, monthly visits, and the study exit visit. Circumferences should be recorded with the zero end of the tape held by the left hand above the remaining part of the tape held by the right hand. The plane of the tape around the body part should be perpendicular to the long axis of the body part being measured.

7.2.2 Detailed Instructions for Mid-Upper Arm Circumference

To locate the midpoint, the participant's elbow is flexed to 90° with the palm facing superiorly. The measurer stands above or behind the participant and locates the lateral tip of the acromion by palpating laterally along the superior surface of the spinous process of the scapula as shown in Figure 7-1. The tape is placed from the acromion process to the tip of the olecranon and the midpoint is marked with a horizontal mark at the midpoint on the posterior surface of the arm as shown in Figure 7-2. The arm is now repositioned to hang loosely at the side with the palm facing the thigh.

The tape is passed around the arm from left to right, and the free and fixed ends are transferred. Ensuring that the tape is at the same level as the mid-upper-arm mark, the measurer tightens the tape so that it touches the skin all around the circumference but does not compress the tissue or alter the contour of the arm. The circumference is then read. Because the arm in cross-section is not an exact circle but rather oval, some difficulty may be met in ensuring that the tape actually touches the skin on the medial side of the arm. If necessary, the middle finger of the left hand can be used to gently press the tape to the skin.

Figure 7-1: Locating Tip of Acromion Process

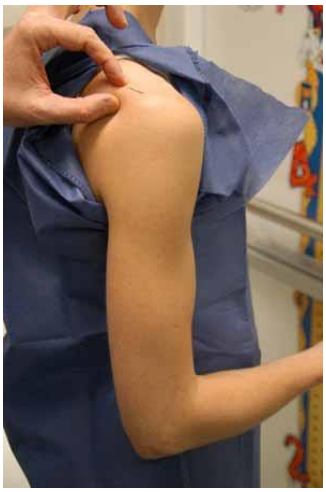
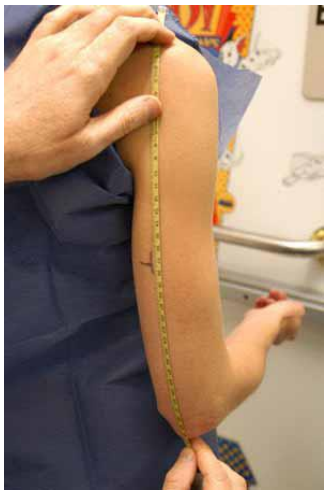


Figure 7-2: Marking Upper Arm Length Midpoint



7.3 Height

In IMPAACT 2001, height will be measured in women at the Entry visit only. This measurement should be carefully performed using a stadiometer, a measuring rod that is attached to many physicians' scales, or other device that is carefully mounted and maintained throughout the study. If no designated equipment is available for measuring height, a tape measure or series of yardsticks could be carefully attached to a wall, with the zero end just touching the floor.

Reminder: Shoes should be removed before height is measured.

For wall-mounted measuring devices, the participant should stand with her back to the device. The participant should be aligned so that the device runs up the middle of the body and standing with heels together and heels, buttocks, and shoulders touching the wall. The participant should tuck her chin down into the chest and stand as tall as possible. If the measuring device has a horizontal bar to assist with the measurement, the bar should be raised above the participant's head and lowered until it just touches the head (the skull; not just the hair). It is important to make certain that the bar is completely horizontal. If the bar is at an angle greater or less than 90° to the wall, the measurement of height will be inaccurate.

If the measuring device does not have a horizontal bar, some surrogate should be constructed to make certain that height is recorded from the point on the measuring device that is exactly horizontal to the top of the center of the head. A plastic right triangle or two pieces of wood attached at a 90° angle could serve this purpose.

Height should be reported in inches or centimeters for women and in centimeters only for infants.

7.4 Weight

Weight should be measured at each visit for women and infants in IMPAACT 2001.

- The same scale should ideally be used for all measurements performed for this protocol. The scale should ideally be calibrated monthly.
- Before the participant is weighed, make certain that the scale is in balance if it is a beam-balance scale or reads zero if it is an electronic scale.
- For women, instruct the participant to stand with both feet centered on the scale with arms at the sides. The participant should not move or hold onto anything during the measurement.
- Allow the scale to stabilize and record the weight in the units provided by the scale (in lbs. or kg form women; in kg only for infants).

7.5 Verification Procedures

The measurer completes and records a full set of circumferences. A second complete set is then measured and recorded. If the difference between any first and second measurement is greater than that allowed under the guidelines, the measurer performs a third circumference measurement.

8.0 World Health Organization (WHO) TB Symptom Screen and TST

8.1 WHO TB Symptom Screen

In IMPAACT 2001, the WHO recommended TB symptom screen is required for confirmed or probable active TB disease. Potential participants with a positive WHO TB symptom screen will be excluded from the study and can only be reconsidered for entry if TB is convincingly ruled out. The WHO TB symptom screen and guidelines from the *WHO 2013 Systematic screening for active tuberculosis* are available at:

http://www.who.int/tb/tbscreening/en/

8.2 Tuberculin Skin Test (TST)

The TST should be performed at screening to confirm eligibility for *HIV-1-infected only* potential participants per inclusion criterion 4.1.3 who do not report having a household contact with known active pulmonary TB and do not have a single positive TST or IGRA at any time in the past per medical records. The TST should be read ideally at 48-72 hours (but can be read up to one week) after administration by a trained observer.

Regardless of TB exposure, a positive TST is defined as follows:
- HIV-1-uninfected – An induration of ≥ 10mm and not redness.
- HIV-1-infected – An induration of ≥ 5mm and not redness.

See detailed directions for administering and reading TST below.

8.2.1 Administering and Reading the TST

A Mantoux TST of purified protein derivative (PPD) will be administered.

A Centers for Disease Control and Prevention (CDC) podcast, which includes sections in administering and reading the TST, can be accessed at:

http://www2c.cdc.gov/podcasts/browse.asp?exactMatch=1&topic=TB+Skin+Test&formsButton=Go%21

Site should follow locally applicable procedures and guidelines for administration of TST. If local guidelines are not available, sites may follow procedures as described in the Clinical Policies and Protocols of the Bureau of Tuberculosis Control of the New York City Department of Health and Mental Hygiene: **https://www1.nyc.gov/assets/doh/downloads/pdf/tb/tb-protocol.pdf**

8.2.2 Reading and interpreting the Tuberculin Skin Test Reaction

The test result should be read only by a trained site investigator. Participants should never be allowed to read their own reaction.

The following procedure should be used to read the reaction:

- Read the result ideally 2-3 days after placement, but it can be read by a trained observer up to 7 days from administration.
- Inspect the injection site for raised areas.
- Palpate the arm for a hard, raised area known as an induration. Feel the edges of the induration with the index finger
- Mark the 2 edges of the induration with a dot, using a black, watermark pen, if available.
- Measure the induration (not redness) at its widest point transversely, from 1 marked edge to the other, using a flexible TST ruler. If the reading is between 2 points, the lower value should be used. Swollen areas, if they feel hard, (but not red areas) should be palpated and included in the measurement.
- Record the size in millimeters and not simply as "positive" or "negative". If there is no induration, record the result as "00 mm."
- Interpret the reaction as positive or negative based on the size of the induration being (≥ 5mm in HIV-1-infected or (≥ 10mm in HIV-1-uninfected).
- Explain the meaning of a positive or negative reaction to the individual and refer for follow-up evaluation, if needed.

NOTE: If the participant fails to return for the scheduled reading but returns up to a week (7 days) after the test, examine the test site and measure any induration present; if it is large enough to be classified as positive, record the result. No further testing is needed. If there is no reaction, there is no need to repeat the test. If the induration is too small to be classified as positive, record the diameter and repeat the test, if feasible. A repeat test can be given immediately.

9.0 Specimen Collection and Laboratory Considerations

The Schedule of Evaluations (SoE) and Laboratory Processing Chart (LPC) are the primary sources of information on specimen collection, processing, testing, storage, and shipping for this study; refer to these documents for further operational guidance as needed.

NIH recommendations for maximum pediatric and adult blood draw volumes will be followed in this study. ***For women, the volume of blood drawn shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period. For infants, the volume of blood drawn at any study visit should not exceed 5 mL/kg in a single day and 9.5 mL/kg over any eight-week period.*** The priority order of sample collections will be as follows: samples needed for clinical safety assessments/AEs will be collected first (specific tests as determined by investigator), followed by samples needed for PK analysis.

It is important that blood draw volumes are documented at each visit and are easily accessible for calculating maximum draw volumes at each visit. Refer to the LPC for shipping information of PK samples.

9.1 Isoniazid, Rifapentine and Desacetyl-rifapentine PK

- Minimum blood volume needed is **1.2 mL**.
- Collect and place into crushed ice.
- Centrifugation and processing can be at room temperature, but should be carried out efficiently and stored within 1 hour of collection at -70°C.
- Prepare **two 0.2 mL** plasma aliquots and store in *separate* cryoboxes.
- Refer to LPC for shipping guidance

9.2 Breast Milk Collection, Processing, and Storage Procedures

9.2.1 Specimen Collection

Equipment: *Clean water and soap*
Two sterile gauze pads
Sterile urine cup with cap or other sterile capped container for milk collection,
One sterile 50 mL conical centrifuge tube

- Before milk collection, both the woman and nurse should wash their hands with soap and water and dry them. The woman should be seated during the collection of breast milk. If a nurse is to assist in the collection, the nurse should also be seated.
- Gently clean the breasts with soap and water. Rinse soap away with clean water and dry the breast with sterile gauze pads. The soap may dry out the skin and could lead to nipple cracks. In those cases, women may not use the soap but should clean the breasts with plain water.
- Observe breasts for any signs of mastitis or other pathology. This information must be recorded on the appropriate CRF.
- Collection of milk can begin. The collection may be obtained from one or both breasts. If milk is collected from both breasts, the milk can be combined in a single container.
- Ask the woman not to touch the nipple, to keep it as clean as possible. She should position her hand on the breast by placing the fingers below and the thumb above the areola. If the breast size is very large, it may be easier to place one hand above and one hand below the breast.

- Place a sterile 50 mL conical centrifuge tube in front of the nipple. A sterile urine cup or other sterile container may also be used for collection, if preferred. It may be easiest if the nurse holds the collection container.
- The woman should express the milk in a manner that is comfortable for her. The woman may prefer to compress her thumb and fingers together while moving the hand away from the chest wall in a 'milking' action towards the nipple.
- Continue to express the milk at a comfortable rate until at least 5mL of breast milk has been collected. If breast milk cannot be collected from one breast, then the procedure should be repeated with the other breast.
- The container with the sample should be capped for transport.
- The nurse should record which breasts were used for collection (left, right, or both) on the appropriate CRF in the comments field.
- Milk samples should be placed in a refrigerator or on crushed ice within 10 minutes of collection and processed within 4 to 6 hours. If processing occurs outside of this window, please note this in the LDMS comments section.

9.2.2 Breast Milk Processing and Storage Procedures

Equipment: *Laminar Flow Hood (Type A, bio-safety hood)*
Centrifuge, Low Speed (capable of 400xg)
Aspiration and transfer pipettes for use with pipet aid (5 and 10mL)
Gloves (latex-free)
Cryovials (screw cap vials)
LDMS labels
Bucket with ice

- Complete processing within 4 to 6 hours of collection. If processing occurs outside this window, please note this in the LDMS.
- Keep the breast milk cold at all times during processing.
- Gently vortex the milk (using the lowest speed) in the capped 50 mL sterile conical tube.
- Prepare two or more, **1.5 mL** aliquots of whole milk in 2 mL cryovials. Discard any extra breast milk.
- Log the samples into the LDMS and label the cryovials with the LDMS generated label (BMK/NON/BMW). Refer to the LPC for shipping information of breast milk PK samples.
- These vials should be kept on crushed ice until frozen and stored at -70ºC or lower.

9.3 Cord Blood PK: Mothers (Optional)

Cord blood will be collected only from women who have received their study drug dose within 72 hours prior delivery. Cord blood collection should be collected into a K3EDTA blood sampling tube and the sample should be treated as per plasma PK samples (refer to IMPAACT 2001 LPC for further instructions). This allows for the blood to be anticoagulated using the same anticoagulant used to validate the assay. All sample labels should contain the time and date of collection as well as the time and date of delivery. Care should be taken when handling the cord blood to prevent splashes, sprays and spills. The use of protective equipment (rubber apron, single use gloves and safety goggles) is required when performing this procedure.

9.3.1 Cord Blood Collection

- The cord blood can be collected using the site's clinic or hospital's collection procedures as long as the safety procedures are followed and contamination of cord blood is avoided.
- If feasible, the cord blood will be collected when delivery takes place in the clinic during the hours when a study nurse is available. However, if it is possible to collect cord blood during off clinic hours, then collect it following your institution's chain of custody procedure.
- There will be no cord blood collection from women who deliver at home or at a non-research facility.
- It is strongly recommended that you use butterfly needle when collecting the cord blood using the needle and vacutainer tube(s). Wipe the umbilical cord with alcohol followed by betadine to remove maternal blood and contaminants before collecting the blood.

9.3.1.1 Cord Blood Collection using Butterfly Needle and Vacutainer Tubes

- After the delivery of the infant, double clamp the umbilical cord and cut the umbilical cord as usual.
  - The first clamp should be applied near the placenta.
  - The second clamp should be applied to the cord on the baby side.
- Cleanse a 4"- 6" area of the umbilical cord with alcohol followed by betadine to remove maternal blood and contaminants (before the delivery of the placenta, if possible).
- Using the butterfly needle and vacutainer tubes, collect 1.2 mL of cord blood, if available
- Collect and place into crushed ice.
- Centrifugation and processing can be at room temperature, but should be carried out efficiently and stored within 1 hour of collection at -70°C.
- Prepare two **0.2 mL** plasma aliquots and store in *separate* cryoboxes.
- Refer to LPC for shipping guidance.

9.4 QUANTIFERON®-TB GOLD IN-TUBE TEST (QFT-GIT OR QGIT)

The QuantiFERON®-TB Gold In-Tube test (QFT-GIT or QGIT) measures IFN-γ production by immune cells following stimulation with mycobacterial peptides.

Tubes are pre-coated by the manufacturer with peptide antigens from certain mycobacterial proteins (ESAT-6, CFP-10, and TB7.7) or controls. Following incubation for 18 to 24 hours, an aliquot of plasma is removed for testing for IFN-γ by ELISA. The test result is determined by comparing the result obtained from the tube containing the mycobacterial stimulation compared with the nil control. A positive mitogen control tube is also used to determine that a valid response is obtainable with the participant's sample and that the assay is performed correctly. Detailed QuantiFERON®-TB Gold (QFT) information and resources are available at: **http://www.quantiferon.com/irm/content/quantiferon-tb-gold1.aspx?RID=300**

A reference library for QFT related information is also available through: **www.gnowee.net.**

QFT instructional videos are available at the following links:

Blood draw and incubation:

http://www.youtube.com/watch?v=TOXF6CzPJYA&list=UUSBDJPFhVjOlD7BJ p44-olQ&index=1&feature=plcp

http://www.youtube.com/watch?v=mpj_q6PDjnk&list=UUSBDJPFhVjOlD7BJp4 4-olQ&index=2&feature=plcp

Reagents and reconstituting
http://www.youtube.com/watch?v=eFI2KiU6e4g&list=UUSBDJPFhVjOID7BJp4 4-oIQ&index=3&feature=plcp

The most current package insert (in English and various language translations) for QGIT can be found at:
http://www.quantiferon.com/irm/content/package-inserts.aspx?RID=347

9.5 Mycobacteriological Studies

Sites should follow their site-specific SOP and use the best locally available method for performing the TB diagnostic tests in adults and infants.

9.6 Sputum Sample Storage/Transport Guidelines

Please refer to the HANC Cross-Network Mycobacteriology Sputum Sample Storage and Transportation guidelines:

https://portal.hanc.info/lab/tbdiagnostics/WorkgroupDocs/Sputum%20Sample%20Storage%20and%20Transport%20Guidelines%20FINAL%202009-10-06.doc

9.7 Coagulation Testing Specimen Collection, Processing and Handling

Blood will be collected for coagulation profile testing in all women at the Screening visit, and at one weekly visit for women who are ≥34 weeks gestational age while taking the study drug regimen. Blood should also be collected for coagulation profile testing during maternal monthly visits if clinically appropriate or indicated by the examining clinician.

9.7.1 Specimen Collection and Processing

9.7.1.1 Preferred Specimen

- One full unopened 3.2% sodium citrate (light blue-top) tube.
- A 9:1 ratio of blood to citrate is critical.
- Mix by gentle inversion 3-4 times. Do not uncap.
- Transport at room temperature within 48 hours.
- Refrigerated and frozen specimens are unacceptable.

9.7.1.2 Alternative Specimen

- 1 mL frozen plasma
- **If transport of the specimen will be delayed longer than 48 hours**, centrifuge the specimen for 15 minutes at 2500-3500 rpm. Using a plastic pipette, remove plasma, taking care to avoid the WBC/platelet (buffy) layer and place into a plastic screw-cap vial and freeze at - 20°C.
- Ship on dry ice.

9.7.1.3 Storage of Alternate Specimen Type (Separated platelet-poor plasma)

- Room temperature: 2 hours
- Refrigerated: 4 hours
- Frozen: - 20°C for 14 days
- Frozen: - 70°C for 6 months

10.0 Expedited Adverse Event Reporting to DAIDS

This section presents information related to expedited adverse event reporting in IMPAACT 2001. Also refer to Section 7 of the IMPAACT 2001 protocol and the following resources:

- DAIDS Table for Grading Adult and Pediatric Adverse Events (DAIDS Toxicity Table), Version 2.0, dated November 2014
- Complications of Pregnancy Section of the Female Genital Grading Table for Use in Microbicide Studies (Version 1.0, dated November 2007)
- Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, dated January 2010
- DAIDS Adverse Experience Reporting System (DAERS) Reference Guide for Site Reporters and Study Physicians
- Package inserts for RPT and INH

All of the above are available on the DAIDS RSC website at:

http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf?sfvrsn=8

10.1 Selected Definitions

Key definitions associated with expedited adverse event reporting in IMPAACT 2001 are provided below. Refer to the Manual for Expedited Reporting of Adverse Events to DAIDS for additional terms and definitions.

Adverse event (AE) The AE definition specified in Section 7.0 of the protocol applies to women and infants enrolled in IMPAACT 2001 beginning at entry into the study (i.e., enrollment in Cohort 1 or Cohort 2). Medical conditions, illnesses, problems, signs, symptoms, and findings identified before entry are considered pre-existing conditions. If a pre-existing condition worsens (increases in severity or frequency) after entry into the study, the worsened condition is considered an AE. If a pre-existing condition resolves after entry into the study but then recurs at a later date, the recurrence is considered an AE.

All AEs occurring among women and infants enrolled in IMPAACT 2001 must be source documented in participant study charts, including the documented assessment of the Investigator of Record (IoR) or designee of the severity of the AE (see Section 7.3.3) and its relationship to each study product the infant has taken (see Section 8.1).

Serious AE (SAE) Medical and scientific judgment should be exercised in deciding whether other AEs not listed in the definition of SAEs in Section 7.3.3 of the protocol should be considered serious. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above should usually be considered serious (ICH E6 and E2A).

SUSAR *Suspected unexpected serious adverse drug reaction*

SUSARs are SAEs that are assessed as both **suspected** and **unexpected:**

- **Suspected** = related ⇒ there is a reasonable possibility that an AE may be related to an investigational agent
- **Unexpected** ⇒ the nature or severity of an AE is not consistent with an investigational agent's current package insert

As indicated in the definitions above, and as shown in Figure 10-1, SAEs are a subset of all AEs, and SUSARs are a subset of all SAEs.

Figure 10-1
Adverse Event, Serious Adverse Event, and SUSAR Subsets

Expedited AE (EAE) *An AE that meets protocol criteria for reporting in an expedited manner to the DAIDS Regulatory Support Center Safety Office*

10.2 AE Severity

The term severity refers to the intensity of an AE. All AEs occurring among women and infants enrolled in IMPAACT 2001 must be assessed for severity on the following scale according to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0, dated November 2014, except for complications during pregnancy:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Potentially Life-Threatening
- Grade 5 = Death

Complications during pregnancy will be graded per the Complications of Pregnancy Section of the Female Genital Grading Table for Use in Microbicide Studies (Version 1.0, dated November 2007) found on the DAIDS RSC website: **http://rsc.tech-res.com/docs/default-source/safety/addendum_1_female_genital_grading_table_v1_nov_2007.pdf**

10.3 AEs that Meet Protocol Criteria for Expedited Reporting (EAEs)

For infants and women enrolled in IMPAACT 2001, EAE reporting requirements are defined in protocol Section 7.3.2 (see LoA #2), and the EAE reporting period is defined in protocol Section 7.3.4.

10.4 AE Relationship Assessment

For purposes of ***toxicity management*** — as specified in protocol Section 8 — the IoR or designee must assess the relationship of all AEs to all study products a woman is taking according to the categories shown in Figure 10-2. The categories are also used when recording AEs on CRFs.

Figure 10-2
Relationship Assessment Categories for Toxicity Management

Relationship Category	Definition
Definitely related	The event and administration of the medication are related in time, and a direct association can be demonstrated.
Probably related	The event and administration of the medication are reasonably related in time, and the event is more likely explained by the medication than other causes.
Possibly related	The event and administration of the medication are reasonably related in time, and the event can be explained equally well by causes other than the medication.
Probably not related	A potential relationship between the event and the medication could exist (i.e., the possibility cannot be excluded), but the event is most likely explained by causes other than the medication.
Not related	The event is clearly explained by another cause not related to the medication.

For purposes of ***EAE reporting***, the IoR or designee must report the relationship of EAEs to the investigational dose of RPT and/or INH according to the categories shown in Figure 10-3.

Figure 10-3
Relationship Assessment Categories for EAE Reporting

Relationship Category	Definition
Related	There is a **reasonable possibility** that the EAE may be related to the investigational dose of RPT and/or INH. Consistent with ICH guidance, the term "reasonable possibility" is intended to convey that there are facts, evidence, or arguments to suggest a causal relationship between the EAE and the investigational dose of RPT and/or INH. Facts, evidence, and arguments that may support a reasonable possibility of a causal relationship include: • A temporal relationship between the EAE and use of the drug • A plausible biologic mechanism for the drug to cause the EAE • Previous reports of similar events associated with the drug (or drugs of the same class) • Resolution of the event after de-challenge (hold/discontinuation of drug) • Recurrence of the event after re-challenge (resumption of drug after a hold) Other potential causes of the EAE (e.g., past medical history, concurrent illness, concomitant medications) should also be considered when assessing whether there is a reasonable possibility that an EAE may be related to the investigational dose of RPT and/or INH.
Not related	There is **not** a reasonable possibility that the EAE may be related to the investigational dose of RPT and/or INH.

Figure 10-4 presents how the five relationship categories used for toxicity management should be mapped to the two relationship categories used for EAE reporting.

Figure 10-4
Mapping of Relationship Categories for Toxicity Management to Relationship Categories for EAE Reporting

Relationship Category for Toxicity Management	Maps To	Relationship Category for EAE Reporting
Definitely related	→	Related
Probably related	→	Related
Possibly related	→	Related
Probably not related	→	Not related
Not related	→	Not related

10.5 EAE Reporting Procedures

All EAEs should be reported to the DAIDS RSC Safety Office using the internet-based DAIDS Adverse Experience Reporting System (DAERS), per instructions provided in the DAERS Reference Guide for Site Reporters and Study Physicians.

The process of EAE reporting via DAERS involves a designated "Study Reporter" creating an electronic EAE report and a designated "Study Physician" reviewing the EAE report, signing the EAE report with an electronic signature, and submitting the EAE report to the DAIDS RSC Safety Office. If an EAE report is not completed and submitted within three reporting days of site awareness that an event meets

EAE reporting criteria, an explanation must be entered in DAERS before the report can be submitted (see the Manual for Expedited Reporting of Adverse Events to DAIDS for the definition of reporting days).

DAERS also may be used to withdraw an EAE report that was submitted in error and to modify or update a previously submitted EAE report.

For all submitted EAE reports, updates must be submitted to report the final or stable outcome of the EAE, unless the original report provided a final or stable outcome. Updates also should be submitted if significant additional information becomes available after an EAE report is first submitted. Significant additional information may include, for example, an updated severity grade or relationship assessment, information on participant status after resumption of one or more study drugs, and/or newly available information on cause of death.

When updated EAE reports are submitted, it is NOT necessary to complete and submit another Event Evaluation CRF (PE6866) to the DMC. Only one PE6866 CRF should be completed and submitted for each event.

DAERS incorporates a report printing function that should be used to print all EAE reports — including modifications and updates — for filing in participant study records. Automated email messages confirming submission of EAE reports also should be printed and filed with the print-out of the associated EAE report.

For questions about DAERS, email **CRMSSupport@niaid.nih.gov**. Questions also may be submitted from within the DAERS application itself.

In the event that DAERS cannot be accessed (e.g., due to poor internet connectivity), paper-based EAE reporting should be used, per instructions provided in the Manual for Expedited Reporting of Adverse Events to DAIDS. Completed paper EAE Forms may be faxed or digitally scanned and emailed to the DAIDS RSC Safety Office. The EAE Form and form completion instructions are available on the DAIDS RSC website; contact details for submission of EAE Forms are provided in the Manual for Expedited Reporting of Adverse Events to DAIDS, which is also available on the DAIDS RSC website.

Appendix I: 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.

- 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.

- 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*.

Appendix II: Sample Informed Consent Coversheet for IMPAACT 2001 Participants

Mother's identifier	
Infant's identifier	
Can the mother read?	☐ Yes ☐ No ⇒ *A literate impartial witness should be present during the entire IC process. Record name and relationship/role of witness below.*
Language of IC process	☐ [Language A] ☐ [Language B]
Version number and version date of informed consent form used during IC process	
Was the IC process conducted per site SOPs?	☐ Yes ☐ No ⇒ *Record and explain departures from site SOPs below.*
Was all information required to make an informed decision provided in a language understandable to the mother?	☐ Yes ☐ No ⇒ *Explain below.*
Were all of the mother's questions answered?	☐ Yes ☐ No ⇒ *Explain below.*
Did the mother comprehend all information required to make an informed decision?	☐ Yes ☐ No ⇒ *Explain below.*
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?	☐ Yes ☐ No ⇒ *Explain below.*
Did the mother choose to provide IC?	☐ Yes ☐ No ⇒ *STOP.*
Date and time at which the mother signed or marked the informed consent form	☐ NA (consent declined, form not signed or marked) **Date:** **Time:**
Did the mother accept a copy of the IC form?	☐ NA (mother chose not to provide informed consent) ☐ Yes ☐ No ⇒ *Offer alternate form of study contact information.*
Notes/Comments	
Signature of study staff person completing informed consent process (and this coversheet)	