IMPAACT

International Maternal Pediatric Adolescent
AIDS Clinical Trials Network

IMPAACT 2026

Manual of Procedures

Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs during Pregnancy and Postpartum

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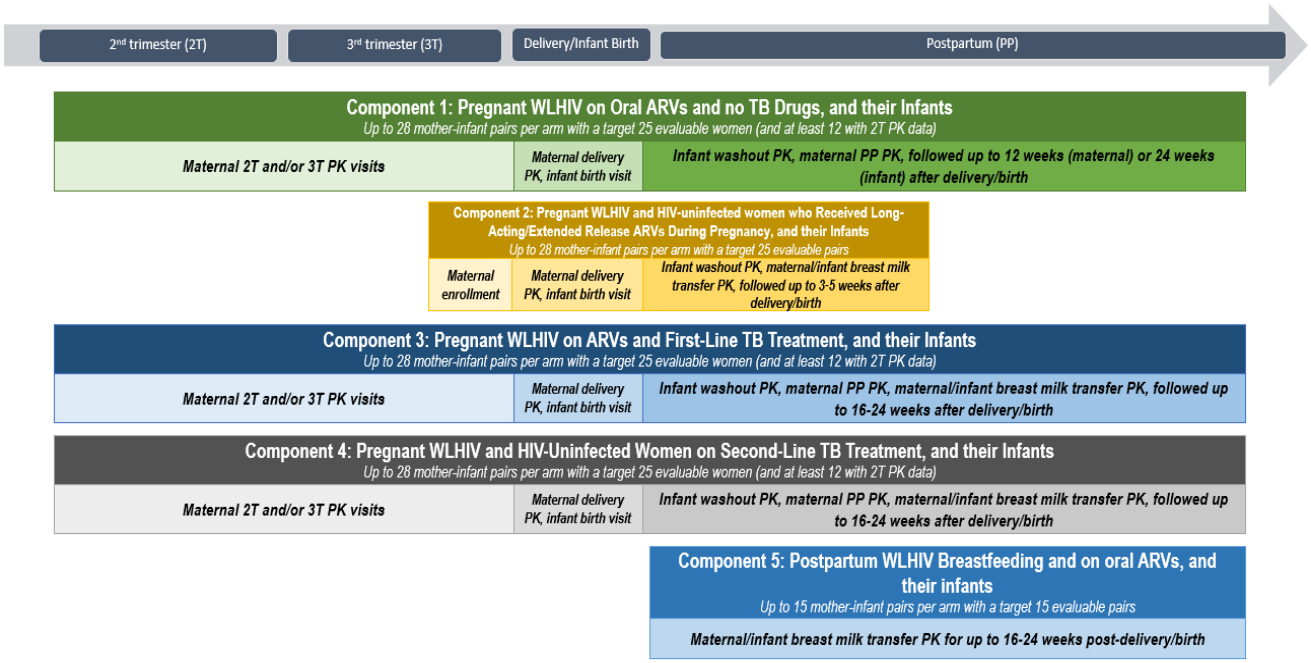
1.0 STUDY OVERVIEW

IMPAACT 2026 is a Phase IV prospective study to describe the PK of antiretroviral (ARV) and anti-tuberculosis (TB) drugs when used alone or in combination during pregnancy or postpartum, among women living with HIV (WLHIV) and HIV-uninfected women, and their infants. The study is comprised of five components which in turn are comprised of arms specific to each drug or drug combination being evaluated; refer to **Error! Reference source not found.** 1-1 for an overview of the study design. Infants born to women enrolled in all components of the study will also be enrolled.

Under protocol Version 1.0, Letter of Amendment #1, up to 325 women and their infants are planned to be enrolled in this study. Each arm in Components 1-4 will enroll up to 28 mother-infant pairs each; arms in Component 5 will enroll up to 15 mother-infant pairs each.

Figure 1-1
IMPAACT 2026 Study Design



This version of the Manual of Procedures (MOP), dated 08 April 2021, reflects the specifications of protocol Version 1.0 dated 22 January 2020 and Letter of Amendment #1 dated 22 March 2021. Study sites should refer to this version for operational guidance upon implementation of Version 1.0, LOA #1 of the protocol.

2.0 PREPARING FOR THE STUDY

2.1 Investigator Responsibilities

IMPAACT 2026 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 *Source Documentation* and *Essential Documents* are useful for interpreting and operationalizing the regulations and guidelines in accordance with DAIDS expectations. These policies are available in the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual at the following website and must be followed throughout implementation of IMPAACT 2026:

https://www.niaid.nih.gov/research/daids-score-manual

IMPAACT 2026 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 the IMPAACT 2026 Protocol Signature Page to formally document his or her agreement to conduct the study in accordance with the study protocol and all applicable protocol-related documents and in compliance with applicable US regulations; the ICH Guideline for GCP; institutional review board/ethics committee (IRB/EC) determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements and institutional policies.

The IoR at each site must also sign a Form FDA 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 Form FDA 1572 are listed on the form, which is available on the DAIDS Regulatory Support Center (RSC) web site:

https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration-forms

IoRs may delegate their obligations and responsibilities for conducting IMPAACT 2026 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 IMPAACT 2026 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 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 (including sIRB) and to request that DRAs and IRBs/ECs note the effective and expiry dates of all approvals. Because IMPAACT 2026 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

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 14.2 and in the *DAIDS Protocol Registration Manual*, which is available at:

https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual

Specific to this study, each IMPAACT 2026 study Component has its own sample ICF. Sites may not necessarily enroll into all study Components; what Component(s) a site is able to enroll to will depend on the study population and drug(s) available at their site. Per the DAIDS Protocol Registration Manual referenced above, sites must submit all ICFs included in the approved protocol to their IRB/EC, or provide written justification for their omission. Therefore, if a site does not intend to enroll into a specific Component of IMPAACT 2026, the site may omit registration of that consent form, but must provide written justification for doing so in the form of a memo to the IRB/EC stating which Components they will enroll into and, therefore, which consent forms they have not included.

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 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 activation procedures with 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 in order to obtain approval to begin study implementation. These requirements are listed on the IMPAACT 2026 Site-Specific Study Activation Checklist, which is available upon request from the IMPAACT Operations Center Clinical Trial Specialists (contact information can be found on the study-specific web page at: https://impaactnetwork.org/studies/IMPAACT2026.asp).

Any questions related to the study activation process should be directed to the IMPAACT Operations Center Clinical Trial Specialists. 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 conducted prior to receipt of an activation notice.

3.0 STUDY-RELATED INFORMATION AND COMMUNICATIONS

All IMPAACT 2026 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 Clinical Trial Specialists of any such inconsistencies.

The IMPAACT 2026 protocol and related protocol documents are available on the study-specific web page:

http://impaactnetwork.org/studies/IMPAACT2026.asp

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

Figure 3-2 lists the study-specific email groups that have been created for IMPAACT 2026. With the exception of the protocol email group (**IMPAACT.prot2026@fstrf.org),** these groups are maintained by the Operations Center Clinical Trial Specialists; please contact the Clinical Trial Specialists to request changes or updates for these groups. For the protocol email group, contact **user.support@fstrf.org**.

Site staff should **avoid** sending messages to the protocol email group (**IMPAACT.prot2026@fstrf.org**) as this group is used for broadcast distribution to all Protocol Team members and study sites. The group is comprised of hundreds of individuals and is not intended to receive site-specific or participant-specific queries. Questions related to interpretation of the protocol or participant management should generally be emailed to the IMPAACT 2026 Core Protocol Team (**IMPAACT.core2026@fstrf.org**) or the Full Protocol Team (**IMPAACT.team2026@fstrf.org**), per the guidelines shown in Figure 3-1.

As indicated in Figure 3-3, active communication is expected between site staff and the Core Protocol Team. When submitting questions and notifications to the Core Protocol 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 3-3. Always retain a copy of correspondence with the Core Protocol Team in the relevant participant's study chart.

Figure 3-1
IMPAACT 2026 Study-Related Communications

Topic	Contact
Adding site staff to the all team and site representatives protocol email group **(IMPAACT.prot2026@fstrf.org)**	**User Support** **user.support@fstrf.org** *(include the protocol number in the subject line of your email message)*
Participant safety; Clinical, adverse events, and management of drug(s) under study, including requests for advice on dose adjustments and additional PK sampling after dose adjustments	**IMPAACT 2026 Core Protocol Team** **IMPAACT.core2026@fstrf.org**
Participant eligibility, potential enrollment of an ineligible participant, and/or deviation from protocol requirements for eligibility determination and/or enrollment	**IMPAACT 2026 Core Protocol Team** **IMPAACT.core2026@fstrf.org**
Co-enrollment issues	**IMPAACT 2026 Core Protocol Team** **IMPAACT.core2026@fstrf.org**
Generic formulation approval of TB/ARV drugs under study	**IMPAACT 2026 Core Protocol Team** **IMPAACT.core2026@fstrf.org** *(include generic approval in the subject line of your message)*
Any aspect of protocol interpretation or study implementation not listed ABOVE	**IMPAACT 2026 Full Protocol Team** **IMPAACT.team2026@fstrf.org**
Data management computer and screen problems	**User Support** **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)*

Figure 3-2
IMPAACT 2026 Email Groups

Email Group	Membership
IMPAACT.team2026@fstrf.org	Individuals listed in the Protocol Team Roster of the protocol
IMPAACT.core2026@fstrf.org	Individuals comprising the Core Protocol Team, per protocol Section 7.1.2.
IMPAACT.team2026investigators@fstrf.org	Site investigators (and designees) from each site participating in the study
IMPAACT.team2026coordinators@fstrf.org	Site coordinators (and designees) from each site participating in the study
IMPAACT.prot2026@fstrf.org	All team and site representatives (also includes all other study-specific groups)

Figure 3-3
Communications with IMPAACT 2026 Core Protocol Team

Questions and notifications for IMPAACT 2026 Core Protocol Team: Copy and paste this listing into the body of your email message to* IMPAACT.core2026@fstrf.org *to help ensure that all required information is included.

Include the protocol number and PID in the subject line of your message.

1. Site number
2. Name of person submitting query
3. Participant type (mother or infant)
4. PID (as applicable)
5. Study Arm
6. Drug(s) under study
7. Age
8. HIV status
9. Reason for query (choose one):
   a. Consultation on eligibility or enrollment (describe in case description)
   b. Consultation on adverse event (describe in case description)
   c. Consultation on management of the drug under study (describe in case description)
   d. Consultation on PK sampling procedures (describe in case description)
   e. Approval for generic formulation of drug under study, refer to Section 4.3.4 (*include generic approval in the subject line of the message)*
   f. Consultation on dose adjustment (including additional PK sampling after dose adjustment)
   g. Other (specify in case description)
10. Current week on study
11. *For mother and infant queries:* currently breastfeeding? (if applicable to study arm)
12. Case description and question or notification for Core Protocol Team

File a copy of the email exchange in the participant's study chart.

4.0 PARTICIPANT ACCRUAL

4.1 Overview

Under protocol Version 1.0 and LOA #1, each arm in Components 1-4 will target enrollment of 25 mother-infant pairs, with a maximum of 28 mother infant pairs per arm. Infants in these arms will be enrolled *in utero.* Component 5 arms will target enrollment of 15 mother-infant pairs, with a maximum of 15 mother-infant pairs per arm.

4.2 Site-Specific Accrual

Sites will be notified of components/arms open to accrual as well as accrual status on the Frontier Science portal. Each arm will open to accrual independently. Sites do not have site-specific accrual targets and may enroll into arms in the study Components **for which they have an IRB/EC-approved site-specific informed consent form registered with the DAIDS PRO**. Once the target or maximum enrollments are reached for a given study arm, that arm will be closed.

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 a condition for study activation, each site will establish an SOP for participant accrual. All sites are responsible for following this SOP, and for updating it if needed, throughout the study accrual period. Component-specific accrual will be tracked by the Core Protocol Team.

The Data Management Center (DMC) will routinely report the number of mother-infant pairs enrolled into each arm at each site — by month and cumulatively — to the Protocol Team. The team will monitor these data in relation to total study accrual and arm-specific accrual targets to determine whether adjustments need to be made to achieve the study objectives most efficiently and to determine when to close each arm to accrual. Similar adjustments may be made in response to SMC reviews of the study.

4.3 Participant Recruitment, Screening, and Enrollment

Refer to protocol Section 4.7 for an overview of the participant recruitment, screening, and enrollment process for this study. Participant recruitment methods may vary across sites but are expected to rely on current patients being seen at a study clinic or from active identification and referral of patients who are taking drugs under study, including individuals participating in other clinical research studies. Sites will be responsible for developing recruitment procedures that are appropriate for their respective local communities, institutions, and IRBs. Because of the importance of obtaining data at every study time point, it is essential that sites realistically consider and explore the likelihood of retention of each potential participant. In particular, it is critical that the site determine to the fullest extent possible that mothers in Components 1-4 will be delivering locally and that there is no precedent or cultural reason for the birth to be elsewhere so that the Delivery and 5-9 Days post-delivery visits may take place within the specified windows.

4.3.1 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. Infants enrolled in Components 1 – 4 will have a PID assigned *in utero*. 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 2026.

Study site staff should assign PIDs from lists provided by the DMC. Sites are encouraged to use lists of PIDs that visually link maternal and infant PIDs whenever possible. Contact the DMC with any questions related to use of PID lists (see the study-specific web page for contact information: https://impaactnetwork.org/studies/IMPAACT2026.asp).

4.3.2 Screening for Eligibility

The component-specific study eligibility criteria are provided in protocol Sections 4.1, 4.2 and 4.3; procedural eligibility screening requirements are described in protocol Sections 6.1 – 6.5. As part of eligibility assessment, women's HIV status may also need to be obtained following the specific methods outlined in protocol Section 4.5. Potential participants who are found to meet all eligibility criteria will be enrolled in the study through the SES as described in Section 4.3.5 of this manual. Participants who are screened but do not enroll in the study for any reason must have the reason for the screening failure documented in source documents.

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 all of the study eligibility criteria are enrolled. Each site must have on file a study-specific SOP for eligibility determination that describes how study staff will fulfill this responsibility; all sites must follow their SOPs when assessing eligibility for all potential participants. **In the event that study staff identify that an ineligible participant has been enrolled**, the Core Protocol Team must be consulted as soon as possible and within no more than 24 hours per the communication procedures described in Section 3 of this manual.

4.3.3 Method of Priority for Gestational Age Calculation

The protocol inclusion criteria for Components 1-4 requires evaluating gestational age. Research site staff should use the Expected Date of Delivery (EDD)/Estimated Date of Confinement (EDC) that is determined by the participant's obstetrical care provider and documented in the medical record. The guidance in this MOP, which is based on ACOG guidelines, may be used as clarification for the local obstetrical care provider in determining EDD/EDC. In the case where a clear determination by the participant's obstetrical care provider is not in the medical record, for example, in the scenario of two different methods of gestational age calculation without obstetrician determination of EDD/EDC, [i.e. last menstrual period (LMP) vs. ultrasound], the best method according to the guidance provided in this section should be used for the purposes of eligibility determination, and should be determined by the participant's clinical obstetrical care provider.

The *first accurate ultrasound* examination of the embryo/fetus, preferably a crown-rump length measurement up to and including 13 6/7 weeks from the first day of the LMP, should be used to confirm or reject the LMP. By convention, the expected date of delivery (EDD) is 280 days after the LMP. If an accurate LMP is available and is consistent (provides a date within the window that *agrees with the earliest accurate ultrasound)*, the LMP should be used to determine gestational age. See Table 4-1 below to determine if dating by LMP is inconsistent with ultrasound measurements to require redating based on ultrasound measurements. For example, if an ultrasound EDD performed at 18 0/7 wk differs from an LMP-derived EDD by 9 days in a particular participant, the LMP derived EDD will be chosen (because a discrepancy of 9 days between the LMP and ultrasound dates is not >10 days used to redate pregnancies with LMP/ultrasound dating discrepancies between 16 0/7 wk and 21 6/7 wk gestational age – Table 4-1). If no accurate LMP is available, use the earliest accurate ultrasound measurements of the embryo/fetus.

Table 4-1: Guidelines for redating Gestational Age Based on Ultrasonography

Trimester	Gestational Age Range based on LMP	Method of Measurement	If Discrepancy Between Ultrasound Dating and LMP Dating	Then eCRF Gestational age
First	≤13 6/7 wk • ≤8 6/7 wk • 9 0/7 wk to 13 6/7 wk	CRL	 More than 5 d More than 7 d	**Use Ultrasound**
Second	14 0/7 wk to 15 6/7 wk	BPD, HC, AC, FL	More than 7 d	**Use Ultrasound**
Second	16 0/7 wk to 21 6/7 wk	BPD, HC, AC, FL	More than 10 d	**Use Ultrasound**
Second	22 0/7 wk to 27 6/7 wk	BPD, HC, AC, FL	More than 14 d	**Use Ultrasound**
Third	28 0/7 wk and beyond[t]	BPD, HC, AC, FL	More than 21 d	**Use Ultrasound**

Abbreviations: AC, abdominal circumference; BPD, biparietal diameter; CRL, crown-rump length; FL, femur length; HC, head circumference; LMP, last menstrual period, d=days

[t] Because of the risk of redating a small fetus that may be growth restricted, management decisions based on third-trimester ultrasonography alone is especially problematic and need to be guided by careful consideration of the entire clinical picture and close surveillance.
See: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/05/methods-for-estimating-the-due-date

In summary, redate (use Ultrasound dating to determine gestational age) as follows:

First trimester: based on CRL measurement
- 8 6/7 wk or less: redate if discrepancy is >5days
- 9 0/7 wk-13 6/7 wk: redate if discrepancy is >7days

Second trimester: based on BPD, HC, AC and FL
- 14 0/7wk-15w6d: redate if discrepancy is >7days
- 16 0/7 wk-21 6/7 wk: redate if discrepancy is >10 days
- 22 0/7 wk-27 6/7 wk: redate if discrepancy is >14 days

Third trimester: based on BPD, HC, AC and FL
28 0/7 wk and beyond: redate if discrepancy is >21days.

In the case of assisted reproduction technology (ART), the ART-derived gestational age should be used for the EDD/EDC using the age of the embryo AND the date of embryo transfer. For example, if the embryo is 3 days old at the time of transfer, the age of the embryo is subtracted from the number of days between ovulation and delivery (i.e. 280-14 = 266 days) to derive an EDD of (266-3 = 263 days) from the date of transfer. Similarly, if the embryo is 5 days old at time of transfer, the EDD will be 261 days from the date of transfer.

4.3.4 Obtaining Approval for Generic Formulations of Drugs under Study

Potential participants may receive innovator (i.e., brand name or non-generic) or generic formulations of ARVs and/or TB treatment drugs under study. The generic formulation of the drug under study must be approved by the Core Protocol Team (see Section 3.0 of this manual for instructions on contacting this group) prior to entry. Sites should make every effort to request approval at least one week prior to the anticipated date of enrollment.

Once a specific generic drug manufacturer formulation is approved, sites are not required to resubmit a request for approval for subsequent participants at any site receiving the same formulation. A list of approved generics will be maintained and available to all sites on the study-specific webpage at:

http://impaactnetwork.org/studies/IMPAACT2026.asp

For generics approval requests for previously unapproved generic formulations, the following items should be submitted when requesting approval and the subject line of the message should state 'generic approval':

1. Generic name of the medication (or medications if it is a fixed dose combination product)
2. Strength of the medication
3. Formulation type (such as, Tablet or Gelcap)
4. Product name used by the manufacturer, if applicable
5. Manufacturer name
6. Location where the product is manufactured, if known
7. Provide a copy of the approved prescribing information or package insert (in English if available, or in another language if it is not available in English).
8. Indicate whether or not this generic formulation is listed on the "WHO List of Prequalified Medicinal Products":
   - The list is available at https://extranet.who.int/prequal/content/prequalified-lists/medicines
   - Type in the name of the generic medicine (for example, "efavirenz") in the INN box, and type the manufacturer's name in the "Applicant" box (for example, "Mylan"), and then click Search. If the medicine is on the WHO List, no additional information is needed (only items 1 – 8). If the medicine is not on the WHO List, please also provide the following information (9-10) below.
9. A copy of the bioequivalence study that was performed for this formulation, if available.
10. If the bioequivalence study results are not available, please provide the name of the regulatory authority which approved the generic formulation and a statement of whether or not a bioequivalence study was required for that approval.

The Core Protocol Team will confirm via email whether or not the specific generic medication is approved for study use at a site. This email must be filed in the site's Essential documents.

4.3.5 Enrolling Eligible Participants

Mother-infant pairs will be considered enrolled in this study upon successful entry of eligibility checklist data into the SES, which will result in generation of Study ID Numbers (SIDs) for the mother and infant. One checklist will be completed per mother-infant pair.

Refer to component-specific sections of protocol Section 6 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.

In particular for Components 1, 3 and 4, it is important to ensure the date of entry will allow PK testing to occur within the parameters specified in the protocol by confirming the following information prior to entry and prior to scheduling the initial PK visit:

- ✓ How long the participant has been taking the drug under study at the required dose (Components 1, 3, and 4 require receiving the drug(s) under study for at least two weeks prior to entry and initial PK)
- ✓ The participant is within the protocol-defined 2nd trimester window (**20 and 0/7 through 26 and 6/7 weeks of pregnancy**) or the protocol-defined 3rd trimester window (**30 and 0/7**

through 37 and 6/7 weeks of pregnancy) visit windows and will still be within these windows at the time initial PK is expected to be scheduled.

- ✓ Initial PK sampling can be performed within 14 days after entry while still being within the 2nd trimester or 3rd trimester protocol-defined windows; if possible, initial PK sampling should be targeted for within five days after entry.

Please contact the Core Protocol Team with any questions involving interpretation of these timelines for any mother-infant pair.

4.3.6 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.

4.3.7 FAQs Related to Enrollment

4-A The protocol specifies that mothers and infants will be enrolled in this study as mother-infant pairs. Will we complete one eligibility checklist for the mother and a separate one for the infant?

For this study, one eligibility checklist will be completed for each mother-infant pair. Separate checklists will not be completed for mothers and infants. Upon successful entry of the checklist into the Subject Enrollment System, the system will generate a study identification number (SID) for the mother and a SID for the infant. Consistent with this approach, infants are considered enrolled in the study at the same time as their mothers (i.e., infants are enrolled *in utero*).

4-B Are pregnant women with multiple gestations excluded? If not, how would we go about enrolling the second twin?

The protocol does not exclude women who are pregnant with multiple gestations. In this case, the second twin should be enrolled in the study as well. To enroll multiple infants to a single maternal PID, place infant PIDs one per box in the last question of the eligibility checklist. Up to 3 infants can be enrolled for each maternal PID in a single checklist. In the unlikely case that there are more than 3 infants, the additional enrollment(s) will need to be performed manually at the Data Management Center (DMC). Please contact the DMC's Randomization Support Office (email **rando.support@fstrf.org** or call +716-834-0900 x7301) and be prepared to provide the PID assigned to the mother and the PID assigned to any additional infants.

5.0 INFORMED CONSENT AND ASSENT

This section contains operational guidance for obtaining informed consent and assent for IMPAACT 2026. This guidance complements but does not duplicate the comprehensive information on informed consent and other human subjects considerations provided in Section 8 of the IMPAACT Manual of Procedures. Please refer to this IMPAACT Manual of Procedures as needed. Also refer to Protocol Section 13.3, Section 4.8 of the ICH Guideline for GCP, and the informed consent section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials as needed.

5.1 Study-Specific Informed Consent

Each study component has its own template informed consent form(s) comprised of two sections:

1. The Master Sample Informed Consent Form, which includes information about the study that is cross-cutting and applies to all sites. Embedded within the Master informed consent for each component is a section where participants must initial to consent for optional genetic testing for themselves and their baby.

2. The Site-specific Consent for Participation will provide site-specific details about implementation and participation.

Additionally, Component 2 has its own template parent/guardian informed consent form comprised of the above two sections, as well as its own template assent form with only one part.

As noted in Sections 2.2 and 4.2 of this MOP, sites are not required to have IRB approved, site-specific versions of every consent form and may choose to only obtain IRB approved, site-specific versions of forms for study Components into which they plan to enroll participants, as long as written justification for this approach is submitted as part of protocol registration.

Sites based in the US may *not* modify anything in the Master section of the informed consent, and will work with the single IRB (sIRB) to modify the Site-specific sections. Sites outside of the US may modify both parts as needed to meet requirements of their local IRB/EC or other institutional policies.

For each study component, there is a single informed consent form to document consent for both mother and infant study participation. Consent must be obtained before any study-specific screening or on-study procedures are performed. Each mother will provide written informed consent for her own and her infant's participation in the study, unless the IRB/EC risk determination for the study requires the consent of both parents or the participant is enrolling in Component 2 and is not legally able to provide her own consent.

- If the IRB/EC risk determination requires the consent of both parents, in addition to the mother providing informed consent for infant participation, the father should also provide informed consent if he is reasonably available at the study clinic. In this scenario, the site would need to adapt the signature pages of their informed consent forms to accommodate both maternal and paternal consent and, if the father is reasonably available at the study clinic, he should document his consent and the date of his consent in the signature block for fathers. If the father is reasonably available at the study clinic, and declines consent, the mother should also not be enrolled in the study. If the father is not reasonably available at the study clinic, this should be documented in source documents and the father's signature block should be left blank. In this case, the mother-infant pair may be enrolled based on the mother's consent.

- For adolescents who wish to join Component 2 and are not able to provide independent informed consent for study participation, consent must be obtained from the parent/guardian. The adolescent must also agree to study participation by signing the Written Informed Assent Form for Participation in Component 2. Should the adolescent reach the legal age of consent during her study participation, an informed consent process must be conducted with the participant. Additional details are available in Protocol Section 13.3.

Informed consent decisions will also be entered into eCRFs.

IMPORTANT NOTE
Per protocol Section 13.3, should the consenting parent or legal guardian of an enrolled maternal or infant participant die or no longer be available for any reason, all applicable IRB/EC policies and procedures should be followed; however, no further study-specific evaluations should be performed until informed consent for continued study participation is obtained from a legally authorized representative/guardian, as defined locally. Study sites may continue to provide care as needed and appropriate (outside of the study), consistent with local standards of care, but no study-specific procedures (outside of the standard of care) may be performed. If a legally authorized representative/guardian cannot be identified, or if the authorized guardian does not consent to continued study participation, the minor participant must be withdrawn from the study. In accordance with the DAIDS policy on *Enrolling Children (including Adolescents) in Clinical Research*, all sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled infant, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

5.2 Assessment of Understanding

The IoR or designee is responsible for providing consenters with all information relevant to their informed consent decisions in a manner that is understandable to them. The consenter should not be asked to make an informed consent decision or to sign or mark an informed consent form or otherwise indicate consent until she fully understands the study. The IoR or designee is therefore responsible for ensuring that each consenter understands all aspects of study participation before obtaining informed consent from them.

A variety of approaches can be taken to assess understanding, and the approach to be used should be specified in site SOPs. One approach uses a semi-structured checklist to guide a discussion in which the consenter responds to open-ended questions designed to elicit their understanding of key concepts. A sample checklist of this type, with accompanying instructions for use, is provided in Section Appendix 5-1. Other approaches may include documented discussions with the consenter as well as structured knowledge assessments administered to the consenter.

5.3 Document the Process

Please refer to Section 8 of the IMPAACT Manual of Procedures and the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials for detailed guidance on documentation requirements. The DAIDS policy includes requirements and suggestions; study sites must comply with all requirements and are encouraged to comply with all suggestions. To assist with compliance, sites may choose to use informed consent coversheets similar to the example provided in Section Appendix 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. All informed consent documentation must be maintained on file in participant study records.

In addition to completing required entries on informed consent forms, each informed consent process should be documented in a signed and dated chart note. For the study informed consent processes, the note should document that informed consent was obtained before any study procedures were performed, and the method used for obtaining consent. 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 as documentation, it is not necessary to transcribe information already documented on the coversheet into the chart note. Informed consent decisions will also be entered into eCRFs.

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

5.4 FAQs related to Informed Consent

5-A What should we do if, during the informed consent process, a mother indicates that she would like to take part in the study but is not willing to undergo certain procedures?

Maternal participants who do not consent to all of the study procedures outlined in the informed consent document are not eligible for the study, unless the procedure the mother is not willing to undergo is the *optional* genetic testing for herself or her baby.

Post-Consent refusal of procedures: The scenario described in this question should be distinguished from an alternate scenario in which a mother indicates that she is willing to undergo all procedures as part of the study informed consent process, but then refuses a procedure later in follow-up. In this scenario, the mother's wishes should be respected. Her refusal should be documented in her study records, and the mother should be asked if she and her infant can continue in follow-up for the full scheduled duration of study participation.

5-B For Component 2, if a minor participant's parent/guardian consents for participation, but the minor indicates during the informed assent session that she feels pressured into joining the study, what should we do?

When enrolling a minor into Component 2, both she and her parent/guardian must agree to study participation in an environment free of coercion. In this case, the minor participant should not be enrolled. Similarly, if the minor expresses a desire to join the study, but her parent/guardian is opposed, enrollment should not proceed. Site staff should approach these situations with care and sensitivity and should help facilitate a conversation between the minor and her parent/guardian when views on study participation do not align.

Section Appendix 5-1
***Sample* Informed Consent Comprehension Checklist for IMPAACT 2026**
[Sites should modify this checklist to be Component-specific]

Mother's (PID) Identifier | |

✓	***1. Please tell me what you understand about this study and why it is being done.***
	To see how much [HIV and/or TB] medicine is in a woman's blood during [pregnancy and/or breastfeeding].
	To look at how much [HIV and/or TB] medicine gets into the baby [after delivery and/or during breastfeeding]
	To see how safe the medicines are for moms and babies.
✓	***2. How long is study participation for mothers and babies?***
	[Components 1, 3 and 4] Mothers will join the study during their second or third trimester of pregnancy and remain in follow up for at least three months after delivery.
	[Components 1, 3 and 4] Babies will stay in the study for about six months after birth
	[Component 2] Mothers will join the study during before giving birth and will stay in the study through delivery.
	[Component 2] Babies will be in the study up to five weeks after birth.
	[Component 5] Mothers and babies will join the study after birth and stay in the study for about 6 months.
✓	***3. What are mothers and babies asked to do if they join this study***
	Mothers and babies who are asked to join may not be eligible to participate
	[Components 1, 3 and 4] Mothers will have up to two study visits during pregnancy and at least one study visit after giving birth.
	[Components 1, 3 and 4] Babies will have three study visits over the course of six months.
	[All Components] Mothers will continue to receive their [HIV and/or TB] medicines from their regular health care providers.
	[All Components] Mothers and babies will both have blood drawn during study visits for routine blood tests and to measure the amount of [HIV and/or TB] medication in their blood. Mothers will also have blood tests to see how well their body is able to fight infection and to check the amount of HIV in the blood.
	[All Components] Mothers will answer questions about themselves and their babies
	Mothers will allow access to their medical records and the medical records of their babies.
	[All Components] Mothers and babies will have physical exams.
	[Components 1, 3, 4 and 5] For three days in advance of most visits, mothers must be able to take their medications at the same time each day and not take their medication on the day of the study visits.
	[All breast milk transfer arms/sites] Mothers will also provide a sample of breast milk at visits after they have given birth, if they are breastfeeding.
	Cord blood sampling of the infant umbilical cord will be done at birth
✓	***4. What are the possible risks for mothers and babies in this study?***
	Risks of blood draws such as discomfort, lightheadedness, infection, or bruising.
	Others may treat mothers/babies unfairly for being HIV-positive or for being in the study.
✓	***5. What are the possible benefits for mothers and babies in this study?***
	There may be no direct benefit.
	Information learned in the study may help others with HIV
✓	***6. What happens if mothers choose not to join the study?***
	Mothers are free to make their own choice about joining or not joining.
	No matter what mothers decide about joining, there will be no effect on access to maternal and child health care outside the study
✓	***7. How will information about mothers and babies be protected?***
	Every effort will be made to keep information private and confidential *(must mention at least one method used by the site)*
✓	***8. What should mothers do if they have questions or concerns about their health, the health of their babies, or what is happening in the study?***
	Must state how to contact study staff.

Outcome *(mark one)*

☐	Mother demonstrated comprehension of all required points
☐	Mother did not demonstrate comprehension of all required points. Not eligible at this date. To be re-completed after re-review of the Informed Consent to demonstrate understanding

Study Staff Signature		Date (DD/MMM/YYYY):

For sites choosing to use informed consent comprehension checklists similar to the sample provided above, the text that follows provides guidance on its intended use. Please contact the IMPAACT Operations Center Clinical Trial Specialists with any questions.

1. The sample informed consent comprehension checklist may be adapted for use at each site, **and the information within should be made Component-specific**.

2. The checklist should be administered after the consenter has completed the informed consent discussion, i.e., after she has read the informed consent form (ICF) or had it read to her and discussed any issues, questions, or concerns she may have. It is generally expected that the checklist will be administered by the same study staff member who conducted the informed consent discussion with the consenter. However, this is not required.

3. The checklist should not be presented to the consenter as a "test," but rather as a way of double-checking that study staff have fulfilled their responsibility to provide all information needed to make an informed decision about taking part in the study. Study staff members who administer the checklist must be sufficiently knowledgeable about the study to make good judgments about consenters' comprehension of the informed consent information. They should be thoroughly familiar with the site-specific ICFs as well as with the content of the comprehension checklists. Role-playing is strongly recommended as part of preparation and training on use of the checklists.

4. Each checklist is structured around open-ended questions that correspond to the required elements of informed consent for research. For each question, at least one "required point of comprehension" is listed on the checklist; for some questions, several required points of comprehension are listed. Each open-ended question should be read to the consenter. Then, through discussion and dialogue, the intent is for the consenter to demonstrate comprehension of all required points of comprehension listed for each question. The consenter should not be expected to state each required point of comprehension using the exact same wording that appears on the checklist. Rather, the consenter should demonstrate *in her own words* that she understands each required point.

5. Because the open-ended questions are to be read to consenters, these questions should be translated into local languages. Sites may also translate the required points of comprehension, but this is not as critical as translating the questions, because the required points of comprehension are not read to consenters.

6. For each question, all required points should be addressed before the study staff member administering the checklist proceeds to the next question. When the consenter demonstrates comprehension of one of the required points, study staff should tick that point in the designated space. If the consenter does not spontaneously address one or more of the required points in her response, study staff should ask another open-ended question to elicit a response about that point.

7. The sample comprehension checklist has been designed to include points of comprehension that address all information required to make an informed decision about study participation. As such, comprehension of all points should be demonstrated before proceeding to the final informed consent decision and signing or marking of the ICF. Sites may choose to modify the wording of the required points of comprehension to correspond with wording used in their site-specific ICFs. Sites may also add points of comprehension to the checklists.

8. When responding to the open-ended questions, consenters may report back more information than is included on the checklist. This is acceptable, as long as the required information is reported back. However, if any misinformation is reported back, study staff should explain the correct information before proceeding to another question.

9. Once administration of the comprehension checklist begins, it is possible that the consenter may spontaneously state many of the required points, without each open-ended question being asked. In such cases, study staff should tick the relevant points on the checklist and then ask the remaining questions or probe about the remaining points that the consenter has not yet mentioned. It is acceptable to ask a question that a consenter may have already answered in her response to a previous question. However, if study staff are confident that a previous response was adequate, the specific question or point does not need to be repeated.

10. It is possible that a consenter might state correct information, yet study staff may not be convinced that she truly understands a required point of comprehension. In such cases, the study staff member should decide if further explanation or discussion is needed before proceeding to the final informed consent decision and signing or marking of the ICF. Further explanation or discussion may take place at the same visit or at another visit. The assessment process may also take place over the course of multiple days if the consenter becomes fatigued and/or if more time is needed for any other reason.

11. Whenever additional information or explanation is needed to help ensure the consenter's comprehension, any informed consent support materials may be used (e.g., the ICF, other visual aids) to help provide the necessary information. After additional information or explanation is provided, open-ended questions should again be asked to confirm the consenter's comprehension of the required points. Some consenters may be more comfortable interacting with the same study staff member throughout the informed consent process and comprehension assessment. However, another staff member may be consulted, if necessary or desired, to help explain difficult concepts and/or respond to specific questions or concerns.

12. The sample comprehension checklist has been designed as a source document, which should be completed, handled, and retained in participant study records like any other source documents. Relevant consenter and participant identifiers should be recorded on the checklists and tick marks for required points of comprehension should be recorded as instructed above. The study staff member who administers the checklist should document the outcome of the assessment in the space provided and should sign and date the checklist on the date of administration. Additional comments may be recorded on the checklist or on an informed consent cover sheet or other site-specific source document per site SOPs; however, such comments are not required.

13. The study staff member who administers the checklist should carefully review it to verify that comprehension of all required points was demonstrated and that this is documented on the checklist (i.e., all required points of comprehension should be ticked). It is recommended that a second study staff member also complete this verification because failure to document comprehension of all required points could be considered an informed consent and eligibility/enrollment violation.

Section Appendix 5-2
Sample Informed Consent Coversheet for IMPAACT 2026

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.*	
Was informed consent obtained prior to conducting any other study procedures?	☐ Yes ☐ No ⇒ *Explain below.*	
Notes/Comments		
Signature of study staff person completing IC process (and this coversheet)		Date (DD/MMM/YYY):

6.0 STUDY VISITS AND PROCEDURES

Protocol Section 6 and the Schedule of Evaluations (SoE) provide comprehensive information on procedural requirements for conducting study visits.

In preparation for each study visit, site staff should review protocol procedures specific to the type of PK sampling to be performed (see Protocol Section 6.10) and provide applicable and timely reminders to participants related to timing and documentation of taking the drugs under study in the days preceding PK visits.

FAQs and other operational tips and reminders related to these protocol specifications are provided in the remainder of this section.

6.1 FAQs Related to Study Procedures

6-A Infant length is listed in the protocol to be measured as part of each scheduled physical examination. Are there standardized procedures that should be followed when measuring length?

All sites should establish SOPs for infant anthropomorphic measurements (length, weight, and head circumference), so that consistent methods are used across infants and across visits for a given infant. Site SOPs are generally expected to follow WHO guidelines, which are available at: **www.who.int/childgrowth/software/en/**.

In particular, in Module B of the WHO's Training Course on Child Growth Assessment, Chapter 4 provides detailed instructions for measuring length.

6-B Women on Component 4 may be taking BDQ three times a week (on Mondays, Wednesdays and Fridays). Prior to intensive PK sampling visits, should timing of BDQ doses be documented for the three days prior to the PK visit, or for three doses prior to the PK visit?

Section 10.3 of the protocol states that the date, time, and amount of the last two **doses** of the drug under study are to be recorded as well as the dose on the day of PK sampling. For BDQ, these doses may not be on concurrent days.

7.0 PARTICIPANT MANAGEMENT CONSIDERATIONS

Per protocol section 8.0, all drugs under study are **provided and managed** by non-study sources (e.g., clinical care providers or investigators of other research studies). It is the responsibility of the clinical care provider or other research study investigator to follow and clinically manage adverse events per the local standard of care or per other research protocol, respectively. Results of IMPAACT 2026 evaluations that are significant for clinical management will be provided to the clinical care provider or other research study investigator for further follow-up. As a requirement for study-specific activation, sites must have an SOP in place on how referrals for evaluation/treatment/management of clinically meaningful findings will take place.

Operational guidance related to dose adjustments based on real-time antepartum PK is provided in Section 7.1; FAQs and operational guidance related to participant management will be added to this section as needs for such guidance are identified.

7.1 Real time antepartum PK and dose adjustments

As described in protocol Section 10.4.2, for select ARVs during pregnancy only, results of individual plasma concentration assays will be reported to site investigators typically within three weeks of sample receipt at the PK testing laboratory. If the PK parameter of interest is below the 10^{th} percentile of non-pregnant adult values, the reports will include a notice to the site investigator that the dose may be sub-therapeutic and that the protocol pharmacologist may be consulted for advice on dosing adjustments. Any such request regarding advice on dosing adjustments should be emailed to the Core Protocol Team per the guidance in Section 3.0 of this MOP. The site investigator should provide the Core Protocol Team with an update on the final determination as to whether a dose adjustment will be made. All dose adjustments will be entered into eCRFs.

For participants for whom a dose adjustment is made, the site investigator may request that a second series of intensive PK plasma samples be analyzed and reported on a schedule agreed upon by the investigator, PK testing laboratory, and protocol pharmacologist. This request should be emailed to the Core Protocol team using the appropriate alias list and following instructions in section 3.0 of this MOP.

8.0 EXPEDITED ADVERSE EVENT REPORTING REQUIREMENTS

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
- Drug(s) under study investigator's brochures and package inserts
- 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.niaid.nih.gov/clinical-research-sites/daids-adverse-experience-reporting-system
https://rsc.niaid.nih.gov/clinical-research-sites/safety-training-resources

9.0 LABORATORY CONSIDERATIONS

Protocol Section 6, the SoE, component-specific Laboratory Processing Charts (LPCs), and the Master Shipping Document are the primary sources of information on specimen collection, processing, testing, storage, and shipping for this study; both clinic and laboratory staff should routinely refer to these resources as needed.

Material/Specimen Transfer Agreements (M/STAs) Non-US study sites and their affiliated laboratories are responsible for obtaining all necessary permits and executing M/STAs as needed to ship specimens to study-specific testing laboratories as listed in the LPC. These requirements must be met prior to study initiation for any *real-time* PK shipments. In addition, efforts to obtain all necessary permits and execute M/STAs for *batched* PK shipments must be initiated prior to study initiation. These items are included in the Laboratory Activation Checklist.

The remainder of this section provides detailed operational instructions for cord blood and breast milk collection. FAQs and other operational guidance will be added to this section as needs for such guidance are identified.

9.1 Cord Blood

Cord blood will be collected per protocol Section 6.10.2, for Components 1, 2, 3 and 4.

Cord blood should be collected into a K2 or K3 EDTA blood sampling tube and the sample should be treated as per plasma or PBMC/DBS PK samples (refer to the component-specific IMPAACT 2026 LPC for further instructions). 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.

9.1.1 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. Collection of cord blood and the maternal delivery sample can be omitted if circumstances prohibit collection (i.e., delivery at non-study facility, delivery during non-business hours). Additional guidance is as follows:

- Components 1, 3 and 4: samples should only be collected if the woman is still being prescribed the drug(s) under study at the time of delivery.
- In addition to plasma, a DBS card will also be stored for women on Arms 1.3, 1.4, and 1.5 (TAF arms) from the cord blood sample.
- If sufficient cord blood volume is obtained and trained personnel are available for processing, PBMCs should also be isolated from maternal and cord blood samples for women on Arms 1.3, 1.4, and 1.5 (TAF arms).

In the event of multiple fetuses, a sample should be collected from the cord of each fetus.

9.1.2 Cord Blood Collection using Butterfly Needle and Vacutainer Tubes

It is strongly recommended that sites use a 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.

- 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 the volume of cord blood as instructed in the LPC.
- Collect and place into crushed ice if only plasma is being isolated from the sample.
    - Samples for DBS, plasma, and PBMC isolation in Arms 1.3-1.5 of Component 1 should be kept ambient.
- Centrifugation and processing for plasma isolation can be at room temperature, but should be carried out efficiently and stored within 1 hour of collection at -70°C or colder.
    - DBS and PBMCs (Arms 1.3-1.5) should be processed/stored as instructed in the Component 1 LPC.
- Prepare plasma aliquots as instructed in LPC.
    - For Arms 1.3-1.5, lysed PBMCs should be stored in a single aliquot and stored in a separate cryobox from plasma and DBS samples collected in this component.
- Refer to LPC for shipping guidance.

9.2 Breast milk

Breast milk will be collected per protocol Section 6.10.4, for Components 2, 3, 4 and 5.

For sites planning to do the breast milk transfer PK sampling, please review Section 6.10.4 to ensure that the mothers and their infants meet the stated requirements at each visit to undergo breast milk sampling.

Breast milk transfer PK sampling involves three single samples collected in parallel: maternal blood, breast milk, and infant blood. The specific timing of the collection of these three samples is described in Section 6.10.4 and in each LPC.

The breast milk collection, processing, and storage procedures for breast milk specimens are described in the following sections.

9.2.1 Breast Milk Specimen Collection

While breast milk sample collection is an essential study procedure, sites should always prioritize women feeding their infants over providing the study-required breast milk samples. This is especially important for women who may be struggling with breast milk supply and infants who are not growing adequately or are sick. During a visit, if an infant is hungry, the participant should first feed her baby and then provide her breast milk sample. In some cases, this may mean that sample collection needs to be delayed until later in the visit than originally planned or that the full volume is unable to be collected.

Sites will need the following supplies to collect the breast milk specimen:
- Clean water and soap, or an alcohol-based hand sanitizer with 60-95% alcohol
- Sterile urine cup with cap or other clean capped container for milk collection

Following are the breast milk collection procedures:
1. Before milk collection, both the woman and clinic staff member assisting her should clean their hands with either soap and water for at least 20 seconds, or with an alcohol-based hand sanitizer with 60-95% alcohol. Clinic staff member should observe breasts for any signs of mastitis or other pathology. This information must be recorded on the appropriate eCRF.
2. Collection of milk can begin. The collection may be obtained by hand expression or using a pump. The participant should fully express all milk from one breast. If the volume collected

is insufficient (less than what is specified in the LPC), the participant should express from the second breast as well. If milk is collected from both breasts, the milk should be combined in a single container.

3. The container with the sample should be capped for transport. Follow the collection instructions as specified in the LPC for the particular Component and visit. Some specimens will require aluminum foil covering during handling due to the light sensitivity of the drug(s) of interest and aliquot storage in amber vials.
4. The nurse should record which breasts were used for collection (left, right, or both) and the method of expression used (hand or pump) on the appropriate eCRF in the comments field.

Note: Milk samples should be placed in a refrigerator or on ice within 10 minutes of collection and processed according to the parameters outlined in MOP section 9.2.2 and the relevant LPC.

9.2.2 Breast Milk Processing and Storage Procedure – Whole Milk

1. Complete processing within the time allowed from collection as specified in the relevant LPC. This can be as short as 1 hour due to the stability of the drug(s) of interest. If processing occurs outside the allowed window, please note this in the Laboratory Data Management System (LDMS).
2. Keep the breast milk cold at all times during processing.
3. Gently vortex the milk (using the lowest speed) in the capped 50mL conical tube.
4. Prepare aliquots as specified in the LPC for the particular Component and visit. . Some specimens will require amber vials due to the light sensitivity of the drug(s) of interest.
5. These vials should be frozen and stored at -70ºC or colder.

10.0 DATA MANAGEMENT CONSIDERATIONS

Refer to protocol Section 11 and the eCRF completion guide developed by the DMC for this study. eLearning modules and other operational guidance on use of the Medidata Rave system for this study are available on the DMC portal. FAQs and other operational guidance will be added to this section as needs for such guidance are identified.

Tables 10-1 and 10-2 below map the **minimum** maternal and infant medical and medication history information specified in protocol Tables 4 and 5 to the eCRFs into which these elements will be entered. Refer to protocol Tables 4 and 5 for the specific data elements that are to be assessed, source documented, and recorded.

Table 10-1
Mapping of Required Maternal Baseline and Interval History Elements to eCRFs

Component	Enter into eCRF
Demographics – All Components	N/A
Medication History	LGW10032: IMPAACT 2026 Medications Log
ARV Medication History	LGW10032: IMPAACT 2026 Medications Log
TB Medication History (Component 4)	LGW10032: IMPAACT 2026 Medications Log
Medical History	MHW10000: Medical History Log (baseline only)
ECG (Component 4)	DGW10041: IMPAACT 2026 Electrocardiogram (ECG) Numeric Results Log DGW10042: IMPAACT 2026 Electrocardiogram (ECG) Variant Results Log
Lab Results	LBW10002: Chemistry/Hematology Test Results Log LBW10082: IMPAACT 2026 HIV-1 Plasma Viral Load (interval only)
HIV Infection History	MHW10000: Medical History Log LBW10053: HIV-1 Plasma Viral Load History Log (baseline only) LBW100094: IMPAACT 2026 Lymphocyte Subset History Log (baseline only)
TB History (Components 3 and 4)	MHW10000: Medical History Log
Obstetrical History	MHW10000: Medical History Log EVW10098: IMPAACT 2026 Pregnancy Record EVW10009: Delivery Record (Infant Enrolled)(Component 5) EVW10043: Labor Record (Component 5) OBW10004: IMPAACT 2026 Pre-Pregnancy Weight
Drugs Under Study	LGW10032: IMPAACT 2026 Medications Log
Concomitant Medications	LGW10032: IMPAACT 2026 Medications Log
Medical Conditions	ADE10006: Adverse Events Log MHW10000: Medical History Log

Table 10-2
Mapping of Required Infant History Elements to the eCRFs

Component	Enter into eCRF
Medical and Medication History	ADE10006: Adverse Events Log Components 1-4) MHW10000: Medical History Log (Component 5) LGW10032: IMPAACT 2026 Medications Log EVW10044: Newborn Exam DGW10041: DGW10041: IMPAACT 2026 Electrocardiogram (ECG) Numeric Results Log DGW10042: IMPAACT 2026 Electrocardiogram (ECG) Variant Results Log LBW10002: Chemistry/Hematology Test Results Log LBW10008: Qualitative HIV-1 Results LBW10082: IMPAACT 2026 HIV-1 Plasma Viral Load
Feeding History	QLW10121: IMPAACT 2026 Infant Feeding Method QLW10122: IMPAACT 2026 Breastfeeding Record

Component	Enter into eCRF
Medical and Medication History	ADE10006: Adverse Events Log MHW10000: Medical History Log LGW10032: IMPAACT 2026 Medications Log EVW10044: Newborn Exam DGW10041: IMPAACT 2026 Electrocardiogram (ECG) Numeric Results Log DGW10042: IMPAACT 2026 Electrocardiogram (ECG) Variant Results Log LBW10002: Chemistry/Hematology Test Results Log LBW10008: Qualitative HIV-1 Results LBW10082: IMPAACT 2026 HIV-1 Plasma Viral Load
Feeding History	QLW10121: IMPAACT 2026 Infant Feeding Method QLW10122: IMPAACT 2026 Breastfeeding Record