

# **IMPAACT 2026**

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

*IND#146,262*  
*DAIDS study ID # 38609*

This file contains the current IMPAACT 2026 protocol,  
which is comprised of the following documents,  
presented in reverse chronological order:

- Clarification Memorandum #2, dated 23 February 2023
- Clarification Memorandum #1, dated 22 October 2021
- Letter of Amendment #1, dated 22 March 2021
- Protocol Version 1.0, dated 22 January 2020

**Clarification Memorandum # 2 for:**  
**IMPAACT 2026**  
**Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis**  
**Drugs during Pregnancy and Postpartum**

**Version 1.0, dated 22 January 2020**

**DAIDS Study ID #38609**  
**IND #146262 Held By DAIDS**

**Clarification Memorandum Date: 23 February 2023**

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### **Summary of Clarifications and Rationale**

The purpose of this Clarification Memorandum (CM) is to:

- Clarify that the required method for collection of infant PK specimens for Components 3 and 4 is venous.
- Clarify that the preferred method for infant PK specimens for Components 1 and 5 is venous however, if this is not possible heel stick may be used.
- Clarify that the infant PK specimen type (venous or heel stick) must be documented on source documents and eCRFs and indicated in the Laboratory Data Management System.(LDMS).
- Clarify that infant nevirapine is not considered a disallowed medication when determining if an infant meets the requirements for washout PK or breastmilk transfer PK sampling.
- Clarify a protocol inconsistency in protocol Section 6 by inserting a description of the Infant 5-9 Day Visit (Component 1) procedures as Section 6.1.5 to align with the Schedule of Evaluations and other protocol procedures.
- Clarify that Component 2 will not accrue participants.

These clarifications do not impact the study design or study-specific procedures.

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### **Implementation**

For all U.S. sites, this CM will be submitted to the Johns Hopkins Medicine Institutional Review Board (IRB), which serves as the single Institutional Review Board (sIRB) for U.S. IMPAACT 2026 sites, for their information. For all sites, IRB/Ethics Committee (EC) approval of this CM is not required by the study sponsor prior to implementation. However, sites may submit this CM to their local IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

This CM and any applicable IRB/EC correspondence should be maintained in each site's essential documents file for IMPAACT 2026. It is the responsibility of the Investigator of Record to ensure that all study staff are made aware of this CM. The content of this CM will be incorporated into any future amendment of the IMPAACT 2026 protocol.

Modifications of protocol text are provided below, generally in order of appearance in the protocol. Where applicable, modified text is shown using strikethrough for deletions and bold type for additions.

1. Section 3.2 Component 2, Pregnant WLHIV and HIV-uninfected women who received long-acting/extended release ARVs during pregnancy, and their infants, the note below is added at the beginning of the section.

**Note: Component 2 will not open to accrual.**

2. A description of the Infant 5-9 Day Visit (Component 1) procedures is inserted as Section 6.1.5 and Sections 6.1.5 and 6.1.6 are renumbered to Sections 6.1.6 and 6.1.7, respectively.

### 6.1.5 Infant 5-9 Days Visit (Component 1)

The infant 5-9 Days visit must take place within 5-9 days after birth. Only infants who meet the requirements for infant washout PK sampling per Section 6.10.3 will complete this visit.

Infant 5-9 Days Visit Procedures (Component 1)		
Clinical		<ul style="list-style-type: none"> <li>• Perform abbreviated physical exam</li> <li>• Update medical and medication and feeding history since last visit per <a href="#">Section 6.9</a></li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	<p><i>For infants undergoing washout PK sampling, collect blood for:</i></p> <ul style="list-style-type: none"> <li>• Infant washout PK sampling per <a href="#">Section 6.10.3</a></li> <li>• <i>For infants for whom informed consent for genetic testing has also been obtained: DBS storage for pharmacogenetics, if not previously collected at the Birth Visit</i></li> </ul>

### ~~6.1.5~~ 6.1.6 Maternal 6-12 Weeks Visit (Component 1)

### ~~6.1.6~~ 6.1.7 Infant 16-24 Weeks Visit (Component 1)

3. Section 6.10.3, Infant Washout PK Sampling: components 1,2,3 and 4, the note below is added after the 2<sup>nd</sup> bullet.

Infants must meet the following requirements to undergo washout PK sampling:

- Birth weight > 1000 grams.
- Not receiving disallowed medications described in [Section 5.4](#)  
*Note: Nevirapine is not considered a disallowed medication for infants. Contact the Core Protocol Team with any questions regarding disallowed medications.*
- No severe congenital malformations or other medical conditions incompatible with life or that would interfere with study participation or interpretation, as judged by the site investigator.
- Components 1, 3 and 4 only: Mother is still receiving the drug under study at the time of delivery and has not missed two or more doses prior to delivery.

4. Section 6.10.4, Mother-Infant Pair Breast Milk Transfer PK Sampling: Components 2, 3, 4 and 5, the note below is added after the b. bullet.

For sites that do not opt out of breast milk transfer PK sampling, mothers and their infants must meet the following requirements at each visit to undergo breast milk transfer sampling:

- Mother-infant pair are breastfeeding at the time of the breast milk PK sampling visit.
- Components 3, 4 and 5 only: Mother is still receiving the drug(s) under study at the time of the breast milk PK sampling visit and has not missed a dose within three days prior to the visit.
- Infant meets the following requirements:
  - a. Birth weight > 1000 grams.
  - b. Infant not receiving disallowed medications described in [Section 5.4](#).  
*Note: Nevirapine is not considered a disallowed medication for infants. Contact the Core Protocol Team with any questions regarding disallowed medications.*
  - c. No severe congenital malformations or other medical conditions not compatible with life or that would interfere with study participation or interpretation, as judged by the site investigator.

5. Section 6.12.1 Specimen Collection, the note below, is added at the end of the section.

**Note: The required or preferred infant PK specimen collection method (venous or heel stick) varies by Component. Infant PK specimen collection method for:**

- **Components 3 and 4 must be venous.**
- **Components 1 and 5 can be venous or heel stick; however, venous is preferred.**

**Every effort should be made to ensure that the same collection method is used for each participant across all sampling time points. The specimen type venous or heel stick must be documented in source documents and eCRFs and indicated in LDMS.**

6. Section 10.3 Pharmacology Data, Table 12, rows two and four are updated.

**Table 1. Documentation Requirements for PK Sampling Data**

<b>PK Sampling Visit Type</b>	<b>Source Document and Enter into eCRFs</b>
Intensive/Sparse PK	<ul style="list-style-type: none"> <li>• Date, time and amount of last two doses of the drug under study prior to observed dose on day of PK sampling, and of observed dose on day of PK sampling</li> <li>• Last two maternal meals and food intake around the observed dose(s), to include dates, times and descriptions</li> <li>• Date and time PK samples drawn</li> <li>• Date, time and amount of last doses of all other medications taken in last 7 days</li> </ul>
Breast Milk Transfer PK	<ul style="list-style-type: none"> <li>• Date, time and amount of last three doses of ARV or TB drug(s) under study prior to PK sampling visit</li> <li>• Last two maternal meals and food intake around the most recent dose(s) before the breast milk sample, to include dates, times and descriptions</li> <li>• Date and time PK samples drawn</li> <li>• <b>Infant PK specimen type: venous or heel stick</b></li> <li>• Infant feeding history</li> </ul>
Cord Blood and Maternal Delivery	<ul style="list-style-type: none"> <li>• Date, time and amount of last doses of all drugs under study before delivery</li> <li>• Date and time of maternal blood drawing</li> <li>• Date and time cord blood obtained</li> </ul>
Infant Washout PK	<ul style="list-style-type: none"> <li>• Date and time PK samples drawn</li> <li>• <b>PK specimen type: venous or heel stick</b></li> </ul>

7. Section 13.5 Potential Risks

The potential risks of participation in this study include risks associated with study procedures. Most study procedures are routine medical procedures that are associated with minimal to no risk in participants. Blood collection **by venipuncture** may cause pain, bruising, swelling, or fainting. There is a very small chance of infection where the needle is inserted. It may be uncomfortable to express breast milk. Blood collection ~~from infants will be done~~ by heel stick, ~~which~~ may cause some discomfort, bleeding or bruising at the site of the heel stick.

**Clarification Memorandum # 1 for:**  
**IMPAACT 2026**  
**Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis  
Drugs during Pregnancy and Postpartum**

**Version 1.0, dated 22 January 2020**

**DAIDS Study ID #38609  
IND #146262 Held By DAIDS**

**Clarification Memorandum Date: 22 October 2021**

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### **Summary of Clarifications and Rationale**

This Clarification Memorandum (CM) clarifies the use of supplements and antacids containing calcium (Ca), iron (Fe), magnesium (Mg), or aluminum (Al) (including prenatal vitamins) in combination with bictegravir (BIC) and dolutegravir (DTG) and the related dietary recommendations for BIC and DTG. These clarifications align with package inserts that have been updated since approval of the current protocol.

In addition, pharmacokinetic (PK) sampling procedures for women (and their infants) who are taking more than one drug under study and thus enrolled into multiple study arms are clarified.

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### **Implementation**

For all U.S. sites, this CM will be submitted to the Johns Hopkins Medicine Institutional Review Board (IRB), which serves as the single Institutional Review Board (sIRB) for U.S. IMPAACT 2026 sites, for their information. For all sites, IRB/Ethics Committee (EC) approval of this CM is not required by the study sponsor prior to implementation. However, sites may submit this CM to their local IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

This CM and any applicable IRB/EC correspondence should be maintained in each site's essential documents file for IMPAACT 2026. It is the responsibility of the Investigator of Record to ensure that all study staff are made aware of this CM.

The modifications included in this CM will be incorporated into the next protocol amendment as specified below.

1. Clarification regarding the use of supplements or antacids containing Ca, Fe, Mg, and Al with BIC and DTG; additions to the text are indicated in bold; deletions are indicated by strike-through.

a.) Section 5.4 Disallowed Medications Prior to PK Sampling

Table 2. Disallowed Medications

Drug Under Study	Disallowed Medications
BIC	<p><u>Anticonvulsants:</u> carbamazepine, oxcarbazepine, phenobarbital, phenytoin  <u>Antimycobacterials:</u> rifabutin, rifampin, rifapentine  <u>Herbal Products:</u> St. John's wort (Hypericum perforatum)  <u>Medications or oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe), unless BIC is administered while fasting a minimum of 2 hours prior to these medications:</u> Calcium or iron supplements, Cation-containing antacids or laxatives, Sucralfate, Buffered medication are <b>not permitted unless the following coadministration instructions are followed:</b></p> <ul style="list-style-type: none"> <li>• <b>Antacids containing Al/Mg: BIC can be taken at least 2 hours before or 6 hours after taking antacids containing Al/Mg. Routine administration of BIC together with, or 2 hours after, antacids containing Al/Mg is not recommended.</b></li> <li>• <b>Supplements (including prenatal vitamins) or antacids containing Ca or Fe: BIC and supplements or antacids containing Ca or Fe can be taken together with food. Routine administration of BIC under fasting conditions together with, or 2 hours after, supplements or antacids containing Ca or Fe is not recommended.</b></li> </ul>
DTG	<p><u>Antiarrhythmic:</u> dofetilide  <u>Anticonvulsants:</u> carbamazepine, oxcarbazepine, phenobarbital, phenytoin  <u>Antimycobacterials:</u> rifampin (ALLOWED for TB arms [Arm 3.1])  <u>Herbal products:</u> St. John's wort (Hypericum perforatum)  <u>Non-nucleosides:</u> delavirdine, efavirenz, etravirine, nevirapine  <u>Protease Inhibitors:</u> atazanavir, darunavir, ritonavir, telaprevir, tipranavir  <u>Medications or oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe), unless DTG administered 2 hours before or 6 hours after these medications:</u> Calcium or iron supplements, Cation-containing antacids or laxatives, Sucralfate, Buffered medications are <b>not permitted unless the following coadministration instructions are followed:</b></p> <ul style="list-style-type: none"> <li>• <b>Medications containing polyvalent cations (e.g., Mg or Al): administer DTG 2 hours before or 6 hours after taking medications containing Mg or Al polyvalent cations.</b></li> <li>• <b>Oral Ca or Fe supplements, including multivitamins and prenatal vitamins containing Ca or Fe: When taken with food, DTG and supplements or multivitamins containing Ca or Fe can be taken at the same time. Under fasting conditions, DTG should be taken 2 hours before or 6 hours after taking supplements containing Ca or Fe.</b></li> </ul>

b.) Appendix III Dietary Recommendations for ARV and TB Drugs

NNRTIs

Integrase Inhibitors

**Dolutegravir/Bictegravir:** May be taken without regard to meals **unless taken at the same time as supplements containing Ca or Fe; in this case, take with food.** (See further dietary instructions in Table 2, Section 5.4)

2. Procedural clarification PK sampling of women (and their infants) receiving more than one drug under study within a Component.

Women receiving more than one drug under study in a single Component will be enrolled into all relevant open arms. The Subject Enrollment System automatically enrolls women into all Component arms they qualify for based on the drugs under study they are receiving at study entry. Women are not given the option to choose the arms within a single Component to participate in. The component informed consent document lists the expected pharmacokinetic draws by drug; by consenting to the Component, the participant is consenting to all applicable draws for the Component. This should be discussed as part of the consent process. Women eligible for and enrolled into multiple arms are expected to undergo PK sampling for all relevant arms, as described in protocol Section 6.10.1. Infants will be enrolled in all arms with their mother. Infant blood volume will not be increased if enrolled in multiple arms and sampling will be indicated per the Schedule of Evaluations (Appendix II-A) and informed consent document.

For example, women receiving a TAF-based regimen and another drug under study (e.g., a co-formulation such as Biktarvy®) in Component 1 will be enrolled into both relevant open study arms and will undergo both intensive and sparse PK sampling procedures relevant to each arm. Infants will be enrolled with their mother in both arms but will only provide the blood volume per sample described in Section 10.3 (i.e. the blood volume per sample will not be doubled if enrolled in two arms). Infants enrolled in a TAF arm (1.3, 1.4 or 1.5) will always have DBS processed from whole blood specimens as described in the protocol, regardless of other study arm participation.)



**Letter of Amendment #1 for:**  
**IMPAACT 2026**  
**Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs during**  
**Pregnancy and Postpartum**

**Version 1.0, dated 22 January 2020**

**DAIDS Study ID #38609**  
**IND #146,262**

**Letter of Amendment Date: 22 March 2021**

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**Information/Instructions to Study Sites from the Division of AIDS**

The information contained in this Letter of Amendment (LoA) affects the IMPAACT 2026 study and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for their review and approval. This LoA will be submitted to the Johns Hopkins Medicine Institutional Review Board which serves as the single Institutional Review Board (sIRB) for US sites for their review and approval. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All applicable IRB/EC and regulatory entity requirements must be followed.

Upon obtaining IRB approval and any other applicable regulatory entity approvals, sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. All required approvals for Letter of Amendment #1 for protocol Version 1.0 must be obtained for site activation.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential document files for IMPAACT 2026. If the IMPAACT 2026 protocol is amended in the future, applicable contents of this LoA will be incorporated into the next version of the protocol.

**IMPAACT 2026**  
**Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs during**  
**Pregnancy and Postpartum**

**DAIDS Study ID #38609**

**Version 1.0, Letter of Amendment #1**

**Letter of Amendment Signature Page**

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Services regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

\_\_\_\_\_  
Signature of Investigator of Record

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Investigator of Record  
(printed)

## Summary of Modifications and Rationale

The purpose of this LoA is to:

- Provide guidance and operational flexibility to safeguard the health and well-being of IMPAACT 2026 study participants in the context of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease 2019 (COVID-19). This guidance is intended for use at sites experiencing disruptions or limitations of usual operations due to COVID-19. This guidance is added as a new appendix to the protocol (Appendix IX).
- Update the safety information for delamanid (DLM), bedaquiline (BDQ), clofazimine (CFZ) and linezolid (LZD).
- Add Expedited Adverse Event (EAE) reporting requirements for  $\geq$  Grade 3 neuropsychiatric adverse events (NPAEs) and  $\geq$  Grade 3 QTcF and QTcF changes  $\geq 60$  ms from baseline collected values.
- Add documentation requirements for communications between the site investigator and the participant's clinical care provider responsible for drug management for enrolled participants.
- Clarify CD4+ cell count and bilirubin laboratory testing requirements.
- Update the monitoring section to reflect current DAIDS policies for clinical site monitoring, which allow for on-site and remote monitoring.
- Remove reference to the DAIDS policy on identification and classification of critical events which has been retired and update the regulatory reporting requirements that still apply for conduct of this study.
- Remove reference to the DAIDS policies - specified below - which have been retired and replace them with instructions for sites that are now contained in the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual.
  - Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials
  - Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials
  - Requirements for Clinical Quality Management Plans
  - Requirements for Manual of Operational Procedures
  - Enrolling Children (including Adolescents) in Clinical Research: Clinical Site Requirements
- Update the NIH and regulatory requirements for entering study results into ClinicalTrials.gov.
- Correct Appendix IV-B Sparse PK Evaluation procedures.
- Update protocol rosters to reflect current membership.

## Implementation

Modifications of protocol text are shown below using strikethrough for deletions and bold type for additions where applicable. Modifications are generally shown in order of appearance in the protocol.

1. Protocol Roster is updated as follows:

To reflect current membership, Mary Elizabeth Smith, Shelley Buscher, Kayla Denson, Lindsey Miller, and Hedy Teppler are removed from the Protocol Roster (deletions not shown). Renee Browning, Kira Bacon, and Madison Cooper are added, as shown below. Renee Browning is also added to the protocol cover page as DAIDS Medical Officer. Brookie Best's role in the study is expanded to include Protocol Pharmacologist in addition to Protocol Vice Chair.

### NIAID Medical Officer

**Renee Browning, RN, MSN**  
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**DAIDS/NIAID/NIH**  
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### Protocol Data Managers

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2. Section 1.4 Second-Line and Newly-Developed TB Drugs with and without ARVs, the first four paragraphs are replaced with the paragraphs below; no change was made to the pharmacokinetic section.

**Based on evidence from a large meta-analysis of an individual patient database to determine relative contributions of individual TB medicines to treatment outcomes, the WHO outlined key changes to treatment of rifampicin-resistant (RR) or multidrug-resistant (MDR) TB in 2018 (77, 128). Second-line TB medicines were regrouped into three categories (A-C) and ranked based on the latest evidence of effectiveness and safety. Bedaquiline (BDQ), fluoroquinolones (levofloxacin [LFX] or moxifloxacin [MFX]) and linezolid (LZD) are in Group A and are recommended as core second-line TB drugs because of their association with improved mortality among people treated for RR/MDR-TB (128). The Group B drugs, namely clofazimine (CFZ) and terizidone (TRD), have been associated with improved treatment outcomes and remain essential in longer treatment regimens for RR/MDR-TB. While delamanid (DLM) was included in Group C due to the paucity of data available to assess efficacy of the drug at that stage (77) DLM is likely to strengthen multidrug TB regimens due to its novel mechanism of action. There is increasing emphasis on improving access to novel agents, such as DLM, and shorter injectable-free regimens containing Groups A and B drugs for people in high-burden programmatic settings, including HIV-infected individuals and special populations such as children, adolescents and pregnant women (79). The 2020 WHO consolidated guidelines for the treatment of drug-resistant TB (129) makes specific reference to use of BDQ during pregnancy, based on programmatic data from a small cohort of pregnant women treated for RR/MDR-TB in South Africa (Loveday 2020). However, data on the safety and pharmacokinetics of most second-line TB drugs during pregnancy and postpartum remain severely limited and use of BDQ and DLM in pregnancy has been specifically identified by the**

WHO as an area for further research (129). Indeed, “pharmacokinetic studies to determine the optimal TB drug dosing and safety (especially in pregnancy)” was highlighted as one of the MDR-TB research priorities by the Guidelines Development Group in 2015 (80).

A paucity of data also exists for potential DDIs between second-line TB drugs and ARVs, particularly in pregnancy. While there appear to be no significant drug-drug interactions between LZD or DLM and ARVs, CFZ, a weak inhibitor of CYP3A4, may potentially increase PI concentrations (81) and BDQ has a number of important DDIs with ARVs used in first and second-line ARV regimens (82).

IMPAACT 2026 will study the PK and safety during pregnancy and postpartum of prioritized core second-line TB drugs, particularly new and repurposed drugs (i.e. BDQ, DLM, LZD, CFZ and fluoroquinolones) and their use in combination with ARVs (where relevant).

### Safety

Despite wide global programmatic introduction of novel and repurposed TB drugs (BDQ, DLM, LZD and CFZ), none of the studies evaluating these drugs have included pregnant women. Reports of treatment safety and outcomes among women receiving these drugs in pregnancy are extremely scarce. While CFZ is known to cross the placenta, it has not yet been associated with teratogenic effects in animals or humans (83) although, Holdiness (in 1989) described 3 neonatal deaths among 13 pregnant women exposed to CFZ (association unclear) (84). Prior to the publication in 2020 of maternal and infant outcomes among 108 pregnant women treated for RR-TB in South Africa (130), only one case report had been published on safety of a drug regimen including LZD and BDQ. Exposure was limited to 3 weeks in the late third trimester of pregnancy in a woman treated for extensively drug-resistant TB (XDR-TB); no fetal/infant toxicities were noted two years after delivery (85). The South African cohort included 20 women who received LZD, 58 who received BDQ and over 40 women who received CFZ at some point during pregnancy. BDQ and LFX were significant predictors for low birth weight among babies exposed to those drugs in-utero however, more research is required to explore this relationship (130). To date, there are no published reports of women receiving DLM during pregnancy.

In non-pregnant adults, use of BDQ, DLM, CFZ and MFX has been associated with prolongation of the QT interval (86) and LZD commonly causes peripheral neuropathy and bone marrow suppression (87). BDQ has also been associated with an increased risk of hepatitis (88). While neuropsychiatric adverse events have been reported among adults receiving treatment for RR-TB disease, these are known side effects of terizidone and high doses of isoniazid and are not usually attributed to DLM. In a prospective cohort of 122 South African participants (52.5% with HIV) with MDR-TB and poor prognosis, treatment outcomes and safety were compared in those who received a BDQ-based regimen (n=82) to those who received a BDQ + DLM-based combination regimen (n=40). There was an increased proportion of psychosis events in adults with MDR-TB receiving DLM + BDQ + optimized background regimen (OBR) compared to those who received BDQ + OBR (without DLM): 6 (15%) versus 3 (3.7%), p=0.02. However, the authors acknowledge that this “was likely associated with higher rates of simultaneous use of terizidone and high-dose isoniazid in the BDQ–DLM combination regimen group” (131).

Unexpected neuropsychiatric adverse effects have occurred in children enrolled in the PHOENIX/A5300B/ IMPAACT 2003B study, which randomized participants to receive either high-dose isoniazid or DLM for prevention of MDR-TB. These have included hypnopompic or hypnogogic hallucinations of visual, auditory, or tactile nature, associated with insomnia or

**nightmares in the majority, and the development of acute psychosis in one participant. Site investigators in this study should refer to the current package inserts for review of side effects related to anti-tuberculosis therapy.**

3. Section 6 Study Visits and Procedures, the 2<sup>nd</sup> paragraph 2<sup>nd</sup> sentence is modified as follows:

All visits and procedures must be documented in accordance with the DAIDS **requirements** policies for source documentation; refer to Section 11 for more information on documentation requirements and entry of eCRFs.

At the end of the section a note is added as follows:

**Note: For sites that may experience operational disruptions due to COVID-19, guidance for study implementation during periods of disruption is provided in Appendix IX.**

4. Section 6.12.2 Specimen Preparation, Testing, Storage, and Shipping, at the end of the section the following paragraph is added:

**Sites using dual platforms for CD4 testing are required to run a CBC with a differential to get a CD4 count. Bilirubin testing includes total and direct bilirubin.**

5. Section 7.3.2 EAE Reporting Requirements for this Study, the first paragraph is modified as follows:

For both women and infants, the SAE reporting category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. In addition to all SAEs, **the following events must also be reported in an expedited manner (i.e. as an EAE):**

- Any Grade 4 or higher hepatotoxicity in mothers or infants.
- Any Spontaneous abortion or fetal death.
- **Any Grade 3 or higher QTcF changes and QTcF changes  $\geq 60$  ms from baseline collected values for ECG results.**
- **Any Grade 3 or higher neurological and psychiatric adverse events (NPAEs) [i.e., abnormal behavior, anxiety, anxiety disorder, depression, depressed mood, restlessness, insomnia, hallucinations, suicidal ideation, psychotic disorder, dizziness, headache, paresthesia, impaired cognition]**

6. Section 7.3.3 Grading Severity of Events (applies to EAE and all other adverse events), the following paragraph is added at the end of the section:

**Grading of ECG results using the QTc (Fredericia) (QTcF) formula for mothers and infants should be guided by the QTc (Bazett) (QTcB) formula grading in the DAIDS AE Grading Table.**

7. Section 8 Participant Management, the last paragraph is modified as follows:

As 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, **and all such communications should be documented in the participant's study records.** With respect to IMPAACT 2026 data collection, adverse events should be entered into eCRFs per Section 7.2.

8. Section 11.1 Data Management Responsibilities, the 1<sup>st</sup> paragraph last sentence is modified as follows:

In maintaining these records, sites must comply with the standards of source documentation specified in the ~~DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials~~ **DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual, which is** (available on the website referenced in Section 11.2).

9. Section 11.2 Essential and Source Documents and Access to Source Data, the 1<sup>st</sup> paragraph is modified as follows:

All DAIDS policies referenced in this section are available at:  
<https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures>. **The DAIDS SCORE Manual is available at <https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations>.**

The 2nd paragraph is replaced with the following:

**Study sites must comply with DAIDS requirements for essential documents and source documentation, as specified in the DAIDS SCORE Manual. This includes establishing SOPs for maintaining essential and source documents. Site SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study, and site SOPs should be followed throughout the study.**

10. Section 11.3 Quality Control and Quality Assurance, the 1st paragraph is replaced with the following:

**Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the DAIDS SCORE Manual, which is available on the website referenced in Section 11.2.**

11. Section 12 Clinical Site Monitoring, the entire section is replaced with the following:

**Under contract to DAIDS or NICHD, site monitors will inspect study site facilities and review participant study records — including informed consent and assent forms, paper-based CRFs (if used), eCRFs, medical records, laboratory records, and pharmacy records — to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. Monitors also will review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by monitors.**

**Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by DAIDS or NICHD.**

**Remote monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity (132). Site investigators will make study documents available for site monitors to review utilizing a secure platform that is 21 CFR Part 11 and HIPAA compliant. Potential platform options include: Veeva SiteVault, Medidata Rave Imaging Solution, Medidata Remote Source Review, site-controlled SharePoint or cloud-based portal, and direct access to electronic medical records. Other secure platforms that are 21 CFR Part 11 and HIPAA compliant may be utilized, as allowed by DAIDS or NICHD.**

12. Section 13.1 Institutional Review Board/ Ethics Committee Review and Approval, the first paragraph is removed and replaced with the following:

**Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific informed consent and assent forms in accordance with 45 CFR 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must promptly report to the IRBs/ECs any changes in the study and must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b) for promptly reporting the following: unanticipated problems involving risks to participants or others; serious or continuing noncompliance with applicable regulations or the requirements or determinations of their IRBs/ECs; and any suspension or termination of IRB approval.**

13. Section 13.2 Vulnerable Participants, the 1<sup>st</sup> paragraph, two references are added to the statement below (see Section 16 changes above):

**The NIH is mandated by law to ensure that pregnant women and children be included in clinical research when appropriate (126, 127).**

The last paragraph is replaced with the following:

**Study sites must comply with DAIDS requirements for enrolling minors in clinical research as specified in the DAIDS SCORE Manual, which is available on the website referenced in Section 11.2.**

14. Section 13.3 Informed Consent, the last paragraph is modified as follows:

Should the consenting parent or legal guardian of an enrolled underage maternal participant or an enrolled infant die or no longer be available for any reason, no further study-specific visits or procedures may be performed until informed consent for continued study participation is obtained from a locally authorized guardian. In accordance with ~~the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research (available at the website referenced in Section 13.2)~~ **requirements for enrolling minors in clinical research (as specified in the DAIDS SCORE Manual)**, all study 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.

15. Section 13.7 Privacy and Confidentiality, the 3<sup>rd</sup> paragraph is modified as follows:

Study sites are encouraged but not required by DAIDS ~~policies~~ to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password protected access systems. Lists, logbooks, appointment



books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

16. Section 14.3. Study Implementation, the section is modified as follows:

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable US, ~~and~~ local and **international** regulations. Study implementation will also be guided by the IMPAACT MOP, study-specific MOP, LPC, and other study implementation materials, which will be available on the study-specific website:  
<https://impaactnetwork.org/studies/IMPAACT2026.asp>

Study implementation at each site will also be guided site-specific SOPs. The DAIDS **SCORE Manual** ~~policy on Requirements for Manual of Operations~~ specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials (available on the website referenced in Section 11.2). These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

17. Section 14.4 Protocol Deviation Reporting; the section is modified as follows:

~~Per the policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials~~ **Per the requirements for source documentation specified in the DAIDS SCORE Manual** (available at the website referenced in Section 11.2), all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to ~~site~~ **applicable** IRBs/ECs and other applicable review bodies in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported within IMPAACT, following procedures specified in the IMPAACT MOP.

18. Section 14.5 Critical Event Reporting is removed as well as the content.

19. Section 14.6 Clinical Trials.gov, the section is renumbered as Section 14.5, and the content in this section is removed and replaced with the following:

**The NIH Policy on Dissemination of NIH-funded Clinical Trial Information establishes the expectation that clinical trials funded in whole or in part by the NIH will be registered and have summary results information submitted to ClinicalTrials.gov for public posting. The protocol team will comply with this policy as well as the requirements of 42 CFR 11.**

20. Section 16 References, references are added to support changes to Sections 1.4, 12, and 13.2 as follows:

128. **Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment Correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet. 2018; 392(10150):821–34. Epub 2018/09/15. [https://doi.org/10.1016/S0140-6736\(18\)31644-1](https://doi.org/10.1016/S0140-6736(18)31644-1) PMID: 30215381.**
129. **WHO Consolidated Guidelines on Tuberculosis. Module 4: Treatment - Drug-Resistant Tuberculosis Treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO**

130. Loveday M, Hughes J, Sunkari B, et al. Seddon J. Maternal and Infant Outcomes Among Pregnant Women Treated for Multidrug/Rifampicin-Resistant Tuberculosis in South Africa. CID 2020 Mar 6; PMID: 32141495
131. Olayanju O, Esmail A, Limberis J, et al. A regimen containing bedaquiline and delamanid compared to bedaquiline in patients with drug-resistant tuberculosis. Eur Respir J 2020; 55: 1901181 [https://doi.org/10.1183/13993003.01181-2019].
132. FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, Updated on January 27, 2021. Accessed at: <https://www.fda.gov/media/136238/download>
133. National Institutes of Health, Guidelines for the Inclusion of Women and Minorities as Subjects in Clinical Research. Federal Register. 1994.
134. National Institutes of Health, NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. 1998

21. Appendix IV-B Sparse PK Evaluation Sampling Time Points, Arms 1.3, 1.4, and 1.5; the sample types in the volumes row have been corrected as follows:

ARMS	Type of PK	REGIMEN(S) BEING STUDIED		
<b>ARM</b>	<b>Type of PK as Indicated in Schedule of Evaluations</b>	<b>COMPONENT 1: ARVS WITHOUT TB DRUGS</b>		
		<i>Sampling during 2<sup>nd</sup> Trimester, 3<sup>rd</sup> Trimester, and 6-12 Weeks Post-Delivery PK Visits, per Appendix I-A.</i>		
1.3	Sparse PK	Tenofovir alafenamide - 10 mg q.d. boosted with cobicistat		
1.4		Tenofovir alafenamide - 25 mg q.d. without boosting		
1.5		Tenofovir alafenamide - 25 mg q.d. boosted with cobicistat or ritonavir		
<b>SPARSE PK SAMPLING SCHEDULE:</b>				
<b>Time Points</b>	<b>Pre-dose</b>	<b>0.5 hrs post-dose</b>	<b>3 hrs post-dose</b>	<b>24 hrs post-dose</b>
<b>Window</b>	No window	±15 mins	±1 hr	±2 hours
<b>Volumes</b>	2 mL (Plasma and DBS)	5 mL (Plasma only)	2 mL (Plasma only)	2 mL (Plasma only)
	6 mL (DBS and PBMC)		6 mL (PBMC)	6 mL (PBMC)

22. Appendix IX is added as follows:

### Appendix IX Guidance for Study Implementation at Sites Experiencing Operational Disruptions Due to COVID-19

To safeguard the health and well-being of study participants in the context of circulating SARS-CoV-2 and the associated coronavirus disease 2019 (COVID-19), the guidance provided in this appendix may be implemented at sites experiencing operational disruptions due to COVID-19.

The extent to which site operations may be disrupted by COVID-19 may vary across sites and over time. All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff. All sites must also comply with any directives received from the study sponsor, the IMPAACT Network, and/or the IMPAACT 2026 Protocol Team. Should a determination be made in the future that the guidance provided in this appendix is no longer applicable, sites will be formally notified and

instructed to inform their IRBs/ECs and other applicable regulatory entities.

#### Visit Scheduling

- Sites are advised to make use of the allowable visit windows specified in protocol Section 6 when scheduling study visits during periods of operational disruption. In the event of a missed visit (i.e., visit not conducted before the allowable window closes), the Core Protocol Team should be contacted for guidance on visit completion on a case-by-case basis.

#### Visit Procedures

- At sites with no capacity to conduct in-person infant visits or where conducting an in-person visit may increase the risk of exposure to SARS-CoV-2, infant medical and medication information and physical exam findings may be obtained through abstraction of available medical records.
- Maternal intensive PK 12-hour and 24-hour samples may be collected within + 2 hours from the targeted timepoint (i.e., the allowable time window is widened from  $\pm 30$  minutes to -30 to + 2 hours).
- If it is not possible to perform local laboratory testing consistent with the site's Protocol Analyte List (international sites), tests may be performed in alternate laboratories using alternative assays (alternate laboratories must adhere to local regulations for clinical laboratory testing).

#### Documentation

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT 2026.
- Documentation should be entered in participant study charts in real-time (or close to real-time) if any of the following occur:
  - Missed visits
  - Out-of-window visits
  - Incomplete or partial visits (document which procedures were performed, and which were not)
  - Remote contacts performed in lieu of in-person visits (document method used to complete the contact and which procedures were performed)
  - Any other participant contacts
  - Use of alternate laboratories or alternate laboratory assays
- In consultation with the Division of AIDS, the IMPAACT Network has developed and disseminated guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures due to COVID-19. Similar guidance will be provided for documentation of use of alternate laboratories or alternate laboratory assays. Please contact the IMPAACT Operations Center Clinical Trials Specialists with any questions related to documentation and reporting requirements.

# IMPAACT 2026

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

### A Study of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network

#### **Sponsored by:**

National Institute of Allergy and Infectious Diseases  
*Eunice Kennedy Shriver*  
National Institute of Child Health and Human Development  
National Institute of Mental Health

#### **Support Provided by:**

Gilead Sciences, Inc.  
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Merck Research Laboratories

**DAIDS Study ID #38609**  
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**FINAL Version 1.0,**  
**22 January 2020**

**IMPAACT 2026**  
**Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During**  
**Pregnancy and Postpartum**

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**Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During**  
**Pregnancy and Postpartum**

**DAIDS Study ID #38609**

**Version 1.0**  
**Protocol Signature Page**

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

\_\_\_\_\_  
Signature of Investigator of Record

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Investigator of Record  
(printed)

**IMPAACT 2026**  
**Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During**  
**Pregnancy and Postpartum**

**ABBREVIATIONS AND ACRONYMS**

2T	second trimester
3T	third trimester
3TC	lamivudine
AAG	alpha-1 acid glycoprotein
ABC	abacavir
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine transaminase
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
ATV/r	atazanavir/ritonavir
AUC	area under the curve
BCRP	breast cancer resistance protein
BDQ	bedaquiline
BIC	bictegravir
b.i.d.	twice (two times) a day
BMI	body mass index
BUN	blood urea nitrogen
CAB	cabotegravir
CAB LA	long-acting injectable cabotegravir
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CES1	carboxylesterase 1
CFR	Code of Federal Regulations
CFZ	clofazimine
CI	confidence interval
CLIA	clinical laboratory improvement amendments
CROI	Conference on Retroviruses and Opportunistic Infections
CRMS	Clinical Research Management System
CV	coefficient of variation
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
DAIDS	Division of AIDS
DAERS	DAIDS Adverse Event Reporting System
DBS	dried blood spots
DDI	drug-drug interaction
DHHS	U.S. Department of Health and Human Services
DLM	delamanid
DMC	Data Management Center
DNA	deoxyribonucleic acid
DRV	darunavir
DRV/r	darunavir/ritonavir

DTG	dolutegravir
DOR	doravirine
EAE	expedited adverse event
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EFV	efavirenz
EIA	enzyme immunoassay
EMA	European Medical Association
EMB	ethambutol
ETR	etravirine
EVA	ethylene vinylacetate
FDA	Food and Drug Administration
FDC	fixed dose combination
FTC	emtricitabine
GCLP	good clinical laboratory practices
Hgb	hemoglobin
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
IM	intramuscular
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IRB	institutional review board
IND	investigational new drug
INH	isoniazid
INSTI	integrase strand transfer inhibitor
IoR	Investigator of Record
IV	intravenous
LCL	lower confidence limit
LDL	low-density lipoproteins
LDMS	laboratory data management system
LFX	levofloxacin
LPC	laboratory processing chart
LPV	lopinavir
LPV/r	lopinavir/ritonavir
LZD	linezolid
M1	glucuronic acid
M2	N-monodesmethyl metabolite
MDR	multi-drug resistant
MDR1	multi-drug resistance 1
MedDRA	Medical Dictionary for Regulatory Activities
MXF	moxifloxacin
MOP	manual of procedures
MTB	mycobacterium tuberculosis
NAT2	N-acetyl-transferases-2
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NRTI	nucleoside reverse transcriptase inhibitor
NNRTI	nonnucleoside reverse transcriptase inhibitor
NVP	nevirapine
OHRP	Office for Human Research Protection

PBMCs	peripheral blood mononuclear cells
PCD	primary completion date
PCR	polymerase chain reaction
P-gp	permeability glycoprotein
PI	protease inhibitor
PID	participant identification number
PK	pharmacokinetic
PLHIV	people living with HIV
PP	postpartum
PRO	Protocol Registration Office
PZA	pyrazinamide
PXR	pregnane X receptor
q.d.	every day/daily
RAL	raltegravir
RBCs	red blood cells
RIF	rifampin
RFB	rifabutin
RNA	ribonucleic acid
RPV	rilpivirine
RR	rifampicin-resistant
RSC	Regulatory Support Center
RTV	ritonavir
SAE	serious adverse event
SD	standard deviation
SDMC	Statistical and Data Management Center
SES	Subject Enrollment System
SID	Study Identification Number
SMC	Study Monitoring Committee
SNP	single nucleotide polymorphisms
SOP	standard operating procedure
SPDSMP	Study Progress, Data, and Safety Monitoring Plan
TAF	tenofovir alafenamide
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir-diphosphate
t.i.w.	three times a week
UCL	upper confidence limit
UGT1A1	uridine diphosphate glucuronyltransferase type 1A1
UN	United Nations
US	United States
VQA	virology quality assurance
WHO	World Health Organization
WLHIV	women living with HIV
XDR-TB	extensively drug-resistant tuberculosis

**IMPAACT 2026**  
**Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During**  
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**IMPAACT 2026**  
**Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum**

**SCHEMA**

- Purpose:** To describe the pharmacokinetic (PK) properties of antiretroviral (ARV) and anti-tuberculosis (TB) drugs administered during pregnancy and postpartum.
- Design:** Phase IV, prospective, open label, non-randomized PK study
- Study Population:** Pregnant and postpartum women living with and without HIV (WLHIV and HIV-uninfected women) receiving ARV and/or TB drugs under study, and their infants.
- Sample Size:** Up to 325 women and their infants across Components and arms:
- Component 1: Up to 28 mother-infant pairs per arm to achieve a target of 25 evaluable women per arm.
- Component 2: Up to 28 mother-infant pairs per arm to achieve a target of 25 evaluable mother-infant pairs per arm.
- Component 3: Up to 28 mother-infant pairs per arm to achieve a target of 25 evaluable women per arm.
- Component 4: Up to 28 mother-infant pairs per arm to achieve a target of 25 evaluable women per arm.
- Component 5: Up to 15 mother-infant pairs per arm to achieve a target of 15 evaluable mother-infant pairs per arm.
- Study Arms:** **Component 1: Pregnant WLHIV receiving oral ARVs and no TB drugs, and their infants:**  
Women  $\geq$  20 weeks gestation NOT receiving TB drugs and receiving one or more of the following oral ARV drugs or drug combinations, and their infants:
- Arm 1.1: Bictegravir (BIC) 50 mg q.d.
  - Arm 1.2: Doravirine (DOR) 100 mg q.d.
  - Arm 1.3: Tenofovir alafenamide (TAF) 10 mg q.d. boosted with cobicistat
  - Arm 1.4: TAF 25 mg q.d. without boosting
  - Arm 1.5: TAF 25 mg q.d. boosted with cobicistat or ritonavir



**Component 2: Pregnant WLHIV and HIV-uninfected women who received long-acting/extended release ARVs during pregnancy, and their infants:** Women  $\geq$  24 weeks gestation who received at least one dose of the following ARV drugs or drug combinations during pregnancy, and their infants:

- Arm 2.1: Long-acting injectable formulation of cabotegravir (CAB LA) any dose

**Component 3: Pregnant WLHIV receiving ARVs and first-line TB treatment, and their infants:** Women  $\geq$  20 weeks gestation receiving first-line TB treatment with at least two of the following TB treatment drugs: isoniazid (INH), rifampin (RIF), rifabutin (RFB), ethambutol (EMB), pyrazinamide (PZA), moxifloxacin (MXF) and one of the following ARV drugs/combinations, and their infants:

- Arm 3.1: Dolutegravir (DTG) 50 mg b.i.d. when combined with RIF or 50 mg q.d. if RIF is not part of the TB regimen
- Arm 3.2: Atazanavir/ritonavir (ATV/r)  $\geq$  300/100 mg q.d. or darunavir/ritonavir (DRV/r)  $\geq$  600/100 mg b.i.d.
- Arm 3.3: Lopinavir/ritonavir (LPV/r) 800/200 mg b.i.d.

**Component 4: Pregnant WLHIV and HIV-uninfected women receiving second-line TB treatment, and their infants:** Women  $\geq$  20 weeks gestation receiving at least one of the following second-line TB treatment drugs, and their infants:

- Arm 4.1: Second-line TB treatment drugs:
  - Levofloxacin (LFX) 750mg – 1000mg q.d.
  - Clofazimine (CFZ) 100mg q.d.
  - Linezolid (LZD) 300mg – 600mg q.d.
  - Bedaquiline (BDQ) 200mg t.i.w.
  - Delamanid (DLM) 100mg b.i.d.
  - Moxifloxacin (MXF) 400mg or 800mg q.d., **and** at least one other second-line TB treatment drug under study

**Component 5: Postpartum WLHIV breastfeeding while receiving oral ARVs, and their infants:** Women post-delivery receiving at least one of the following oral ARVs, and their infants:

- Arm 5.1: ATV/r
- Arm 5.2: DRV/r
- Arm 5.3: LPV/r

**Study Duration:**

Approximately 5 years total. Each arm will open to accrual independently and will accrue independently and over approximately 36 months from the first enrollment in each arm, and participants will be followed as follows:

- Components 1: Up to 12 weeks after delivery for mothers and up to 24 weeks after birth for infants.
- Component 2: Up to 5 weeks after delivery for mothers and infants.
- Components 3, 4 and 5: Up to 24 weeks after delivery for mothers and infants.

## Primary Objectives

### Component 1:

- To describe the PK parameters during pregnancy of selected ARV drugs administered to WLHIV who are not receiving TB drugs, and to compare these parameters to (a) historical PK data from non-pregnant women and (b) each participant's own postpartum PK data.

### Component 2:

- To describe the kinetics of (a) placental and breast milk transfer of CAB LA from mother to fetus/infant and (b) infant elimination of CAB LA acquired across the placenta after maternal dosing during pregnancy.

### Component 3:

- To describe the PK parameters during pregnancy and postpartum of selected ARV drugs and first-line TB treatment drugs co-administered to WLHIV.

### Component 4:

- To describe the PK parameters during pregnancy and postpartum of second-line TB treatment drugs administered to WLHIV and HIV-uninfected women.

### Component 5:

- To describe the kinetics of drug transfer of selected ARVs from mother to infant via breast milk.

## Secondary Objectives

### All Components:

- To describe maternal and infant safety and clinical outcomes.

### Components 1, 3 and 4:

- To compare drug concentrations in plasma from cord blood with concentrations in maternal plasma at delivery for selected ARV and/or TB treatment drugs.
- To describe the neonatal elimination of selected ARV and/or TB treatment drugs acquired across the placenta after maternal dosing during pregnancy.

### Components 3 and 4:

- To describe the kinetics of drug transfer of selected ARVs and/or TB treatment drugs from mother to infant via breast milk

### Component 4:

- To describe the PK parameters of selected ARVs when co-administered with selected second-line TB treatment drugs to WLHIV during pregnancy and postpartum.

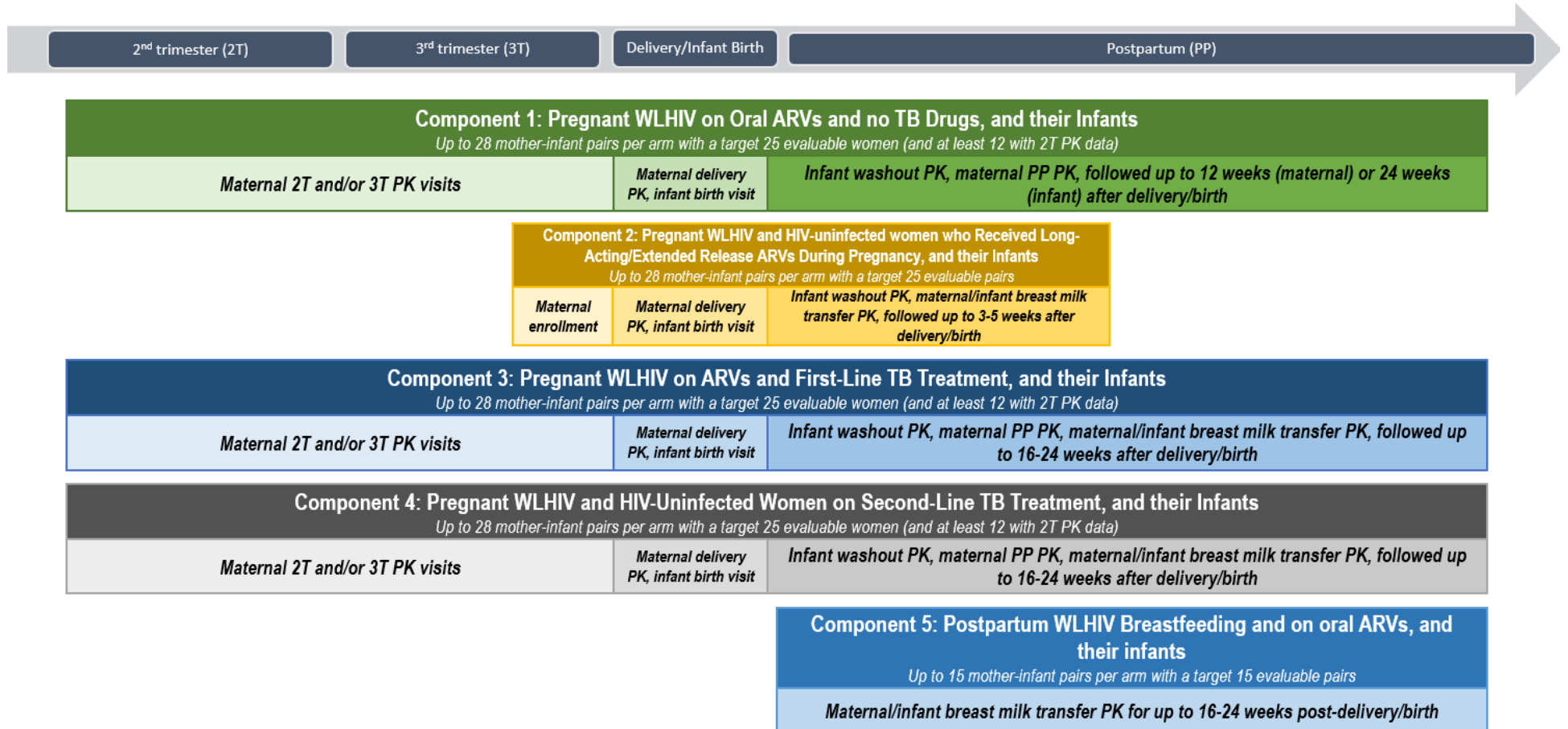
**Other Objectives**

- To assess plasma protein binding of highly bound ARVs and/or TB treatment drugs during pregnancy and postpartum.
- To explore genetic sources for variability in drug exposure in pregnant and postpartum women and their infants for selected ARV and/or TB treatment drugs.

# IMPAACT 2026

## Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum

**Figure 1**  
**Overview of Study Design**



# 1 INTRODUCTION

## 1.1 Background

Clinical trials studying the pharmacokinetics, during pregnancy and/or postpartum, of antiretroviral (ARV) and tuberculosis (TB) drugs are limited. The development of appropriate ARV and TB drug regimens in pregnant and postpartum women is critical to providing optimal care to women living with human immunodeficiency virus (HIV) and/or TB, and their infants. Overdosing may lead to maternal adverse events and increased risk of fetal toxicity. Underdosing may lead to inadequate virologic or mycobacterial control, increased risk of development of drug resistance mutations and a higher rate of perinatal HIV and TB transmission. The effect of pregnancy on both drug disposition and immune function can leave the mother at risk for viral/mycobacterial breakthrough and progression of disease, putting pregnant women at particular risk for progression of HIV and TB disease. Pregnancy produces a temporary physiologic and immunologic homeostasis between tissues that are antigenically different. One component of the maternal accommodation of the fetus is partial suppression of the maternal immune system with an elevation of glucocorticoids, which are also implicated in inducing hepatic metabolism as one component of this response (1). Understanding the kinetics of transmission of ARV and TB treatment drugs from mother to infant via breast milk is also critical. While the infant dose via breast milk is often small, immaturity of infant clearance pathways may lead to slow excretion and accumulation to biologically significant concentrations, as has been shown for nevirapine (NVP), lamivudine (3TC) and emtricitabine (FTC) (2, 3).

Studying the drug interactions between ARVs and TB treatment drugs is also important to ensure safe and effective use of these drugs in pregnant and postpartum women. While pharmaceutical companies rarely undertake clinical trials in pregnant women, obtaining data on how pregnancy affects drug exposure remains a priority for the International Maternal Pediatric Adolescent Clinical Trials (IMPAACT) Network so that safe and effective doses of ARVs and anti-tuberculin medications for pregnant women can be prescribed.

The predecessor study to IMPAACT 2026 is IMPAACT P1026s, a Phase IV, prospective PK study of selected ARV, TB and related drugs during pregnancy and postpartum. Since 2003, P1026s has helped to address these gaps, but there remains an ongoing need to obtain pregnancy and postpartum PK data on newly approved drugs and drugs for which data are lacking on interactions with TB drugs.

## 1.2 Clinical Pharmacology During Pregnancy

Women have been underrepresented in clinical drug trials, and pregnant women are generally excluded from drug development programs (4). Recent investigations demonstrate that pharmacokinetic (PK) parameters may differ in men and women, and that women may display distinct therapeutic and toxic responses to specific compounds. One area of active investigation is the impact of gender on hepatic drug metabolism. Women demonstrate increased clearance of various drugs (e.g. verapamil, diazepam, and midazolam) when compared to men owing to enhanced cytochrome P450 (CYP) isozyme activity (5, 6). Many antiretroviral agents, including protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized by CYP pathways. An understanding of the impact of gender differences on the metabolism of these drugs is needed to maximize efficacy and minimize toxicity of these agents when used in women (7-9).

Pregnancy may have an additional profound effect on drug disposition. Pregnant women experience unique physiological changes that may result in clinically significant alterations in drug pharmacokinetics and pharmacodynamics. These changes begin early in gestation and include: (a) increased gastrointestinal transit time that can alter the rate and extent of drug absorption; (b) large changes in total body water and fat, increasing drug distribution volume; (c) decreased albumin and increased alpha-1 acid glycoprotein (AAG) concentrations that may cause clinically relevant changes in drug protein binding; (d) increased cardiac output, ventilation, and hepatic and renal blood flow which may impact drug metabolism and elimination; and (e) increased concentrations of endogenous glucocorticoids that may affect the activity of hepatic enzyme systems that regulate drug metabolism (1, 10-14).

Placental drug transport is another critical aspect of perinatal pharmacology for which few data exist for many antiretrovirals. Transport of antiretroviral agents from mother to fetus may provide protection of the fetus against HIV infection across the placenta and at the time of birth but may also expose the fetus to the risk of toxic drug effects. Placental drug transfer may be studied by several techniques, all of which have advantages and disadvantages. *In vitro* methods, such as isolated perfused placenta preparations, are convenient but may not accurately reflect *in vivo* conditions. Chronically catheterized non-human animal models allow complete characterization of the relationship between maternal and fetal concentrations, but interspecies differences limit the extrapolation of these findings to humans. Human studies are limited to comparisons of the ratio of maternal drug concentrations, at the time of delivery, to those in cord blood. While this ratio provides information about only a single point in time, it is the only technique currently available for humans and, for now, is the most useful.

Newly licensed and investigational ARV drugs being evaluated in this study are briefly summarized below.

### 1.2.1 Bictegravir

Bictegravir (BIC) is a potent integrase strand transfer inhibitor (INSTI) with a high genetic barrier to resistance. BIC does not require boosting and is dosed once-daily. It was approved by the Federal Drug Administration (FDA) in Feb 2018 as a component of a three-drug fixed dose combination (FDC) ARV regimen consisting of BIC [50 mg], FTC [200 mg], and tenofovir alafenamide (TAF) [25 mg]. Gilead Sciences has entered into licensing agreements to allow for production of BIC-containing regimens by international generic drug manufacturers and for the distribution of BIC as a single agent or part of an FDC for distribution in 116 developing countries (10).

In PK studies, the median half-life of BIC was found to be 17.3 hours (IQR 14.8-20.7) with  $T_{max}$  achieved at 2.0-4.0 hours post administration. In PK studies among people living with HIV (PLHIV), following oral administration of BIC/FTC/TAF, mean BIC  $C_{max}$ ,  $AUC_{tau}$  and  $C_{trough}$  respectively were 6.15  $\mu\text{g/mL}$  [percentage coefficient of variance (CV%) 22.9], 102  $\mu\text{g} \times \text{h/mL}$  (CV% 26.9) and 2.61  $\mu\text{g/mL}$  (CV% 35.2). BIC is highly bound to plasma proteins (>99%) and metabolized via CYP3A and uridine diphosphate glucuronyltransferase type 1A1 (UGT1A1) pathways with 60% excretion in feces and 35% in urine. As a substrate of CYP3A and UGT1A1, BIC levels can be lowered by drugs known to be potent CYP3A and/or UGT1A1 inducers, including carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, and rifapentine. In a drug-drug interaction (DDI) study, rifampin co-administration resulted in a 75% decrease in BIC  $AUC_{0-24h}$ , while rifabutin resulted in a 38% decrease (11). In a Phase I study, BIC PK results were compared between individuals co-administered rifampin and twice daily dosing of BIC/FTC/TAF versus individuals receiving once daily dosing of BIC/FTC/TAF only.

Compared to BIC/FTC/TAF once daily dosing, rifampin co-administrated with twice daily dosing of BIC/FTC/TAF resulted in BIC AUC<sub>0-24h</sub> and C<sub>trough</sub> reductions of ~ 60% and 80%, respectively (12). Therefore, BIC co-administration with rifampin is not recommended. BIC acts on the organic cation transport-2 (OCT2) and the multidrug and toxin extrusion transporter-1 (MATE1), inhibiting clearance of dofetilide, an antiarrhythmic drug. Therefore, dofetilide should not be used by persons taking BIC. In vitro experiments demonstrated that co-administration with St. John's wort lowers BIC levels, as does co-administration with supplements containing polyvalent cations such as calcium, iron, laxatives, antacids or buffered medications. Co-administration of BIC/FTC/TAF with metformin can increase metformin levels.

The safety of BIC, as a component of BIC/FTC/TAF, has been evaluated in treatment naïve PLHIV and PLHIV who switched to BIC/FTC/TAF in randomized controlled blinded clinical trials led by Gilead Sciences. The most common adverse reactions in treatment naïve PLHIV initiating BIC/FTC/TAF were diarrhea, nausea, and headache reported by up to 5% of participants, with < 1% of persons in the clinical trials discontinuing BIC/FTC/TAF due to adverse events. In one of these trials, nausea was noted to occur significantly less frequently among PLHIV initiating BIC/FTC/TAF compared to those initiating dolutegravir(DTG)/lamivudine(3TC)/abacavir(ABC) (10% vs 23% respectively; p<0.0001)(13). However, the increased incidence of nausea was attributed to the ABC/3TC component versus the FTC/TAF component, and was not attributed to differences between BIC and DTG (13). Among adults randomized to BIC/FTC/TAF, bilirubin elevation was the most common lab abnormality occurring in 12% of participants, compared with graded bilirubin events occurring in 4% and 6% of participants randomized to DTG/ABC/3TC or DTG/FTC/TAF respectively. However, all gradable bilirubinemia events among BIC/FTC/TAF participants were restricted to the Division of AIDS (DAIDS) Grade 1 or 2 events. Elevations in liver function enzymes (alanine transaminase [ALT], aspartate aminotransferase [AST], Amylase), creatinine kinase, and low-density lipoproteins (LDL) occurred in 2-4% of study participants receiving BIC/FTC/TAF and these proportions were similar to events in the arms receiving DTG/3TC/ABC and DTG/FTC/TAF. Among BIC/FTC/TAF recipients, baseline creatinine increased 0.1 mg/dL by 4 weeks of treatment, remaining stable through 48 weeks of treatment and this finding was comparable to creatinine increases observed in the ABC/DTG/3TC and DTG/FTC/TAF groups. BIC/FTC/TAF is not recommended for use in persons with creatinine clearance (CrCl) of ≤ 30 mL/min or in persons with severe hepatic impairment (Child-Pugh Class C). While the potential for immune reconstitution exists, Phase III clinical trials conducted thus far have enrolled fewer treatment naïve PLHIV with low CD4+ cell counts. In an international Phase III randomized clinical trial exclusively enrolling women to evaluate the safety and efficacy of switching to BIC/FTC/TAF among virologically suppressed participants receiving an INSTI or Protease Inhibitor-based (PI) based regimen, switching to BIC/FTC/TAF was found to be non-inferior based on viral suppression at 48 weeks and the regimen was well tolerated (14). There have been no human studies of BIC use in pregnancy. Animal studies of BIC in pregnancy have not detected any significant birth defects or other safety concerns. BIC was detected in the plasma of nursing rat pups on postnatal day 10, likely due to the presence of BIC in milk.

### 1.2.2 Doravirine

Doravirine (DOR) is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) approved by the FDA in August 2018. DOR has antiviral activity against wild-type HIV-1 and variants with the most frequently transmitted NNRTI-resistance mutations. DOR is available in two formulations: (i) a once-daily tablet for use in combination with other antiretroviral agents (Pifeltro) (15), and (ii) a once daily fixed-dose combination with 3TC and tenofovir disoproxil fumarate (TDF) (Delstrigo) (16). There are no data available describing use of doravirine in

pregnant humans. Reproductive toxicology studies in pregnant and lactating rabbits and rats revealed no effects on fetuses or newborns exposed to DOR (15).

A randomized, Phase III, non-inferiority trial comparing DOR 100 mg with ritonavir-boosted darunavir, both given with two nucleoside reverse transcriptase inhibitors (NRTIs), was conducted in adults with previously untreated HIV-1 infection (17). At week 48, 321 (84%) participants in the DOR group and 306 (80%) in the darunavir group achieved plasma HIV-1 RNA < 50 copies/mL indicating non-inferiority of the DOR-containing regimen. The most commonly reported adverse events in the DOR arm were diarrhea (5%), nausea (7%), and headache (6%). The incidence of skin rash and neuropsychiatric events was similar between the DOR and darunavir groups. Overall, 19 of 383 (5%) participants in the DOR arm had serious adverse events, but these were considered drug-related in only one participant in whom nausea and vomiting resolved after 4 days without dose interruption or modification. In a separate study, a single oral suprathreshold dose of DOR (1200 mg) did not cause clinically meaningful QTc interval prolongation in healthy adults (18).

DOR is eliminated primarily by CYP3A-mediated metabolism (19). The predominant metabolite, which is generated by oxidative metabolism, does not possess antiviral activity based upon *in vitro* studies (20). Mass-balance studies with single oral dose and single intravenous (IV) dose DOR have been conducted in healthy volunteers (20). Following oral administration of [<sup>14</sup>C]DOR, 10.8% of the dose is eliminated in the urine and 90.4% is eliminated in the feces. Following IV administration, clearance and volume of distribution were 3.73 L/h (95% confidence interval [CI]: 3.09, 4.49) and 60.5 L (95% CI: 53.7, 68.4), respectively, suggesting that DOR is a low intrinsic clearance drug which distributes into tissues. DOR is not highly bound to plasma proteins (unbound fraction 0.24).

DOR is a substrate for CYP3A (21). Accordingly, DOR exposure is increased upon co-administration of CYP3A inhibitors and decreased upon co-administration of CYP3A inducers (21, 22). Further, *in vitro* data suggest that DOR is a substrate for p-glycoprotein (20). However, excretion of unchanged DOR in urine and bile is not significant and the clinical relevance of transporter-mediated interactions is unknown. Food effects are not expected to be clinically meaningful. In two open-label, single-dose, randomized, two-period, crossover trials in healthy volunteers, no clinically important differences were observed in DOR area under the curve (AUC) and C<sub>max</sub> between the fed and fasted states (23).

### 1.2.3 Tenofovir Alafenamide

TAF, a newer prodrug form of tenofovir (TFV), exhibits greater stability in plasma than TDF, resulting in higher cell loading and ~86-91% lower TFV plasma concentrations (24), which leads to lower risk of renal and bone toxicity with long-term use (25-27). Following oral ingestion, TAF reaches peak concentrations ~0.5 hours post-dose and has a half-life of ~0.4 hours (24). Plasma TAF moves rapidly into cells where it is catalyzed to TFV by carboxylesterase 1 (CES1) in the liver and cathepsin A in immune cells/tissue. Intracellular TFV then undergoes phosphorylation by intracellular kinases to its active form, tenofovir-diphosphate (TFV-DP). TFV-DP exhibits a half-life of ~3-6 days in peripheral blood mononuclear cells (PBMC) (28, 29) and ~17 days in red blood cells (RBCs) (28, 30). PBMC concentrations of TFV-DP are ~7-fold higher with TAF 25 mg (24) and ~2.4- to 4-fold higher with cobicistat-boosted TAF 10 mg in comparison to TDF 300 mg (31, 32). With daily TDF administration, steady-state TFV-DP concentrations in PBMCs are generally in the range of 90-200 fmol/10<sup>6</sup> cells (28, 33-35) and ~130 fmol/10<sup>6</sup> cells in RBCs (28). With daily TAF administration, median (range) TFV-DP concentrations in PBMCs are 488 (295-752) fmol/10<sup>6</sup> cells (36).



Due to the long intracellular half-life of TFV-DP in RBCs, multiple studies have examined the utility of TFV-DP in dried blood spots (DBS) as a measure of cumulative adherence to TDF-based therapies. TFV-DP concentrations in DBS have been examined with efficacy outcomes in multiple HIV prevention (37-40) and treatment (41, 42) studies. TFV-DP shows a 25-fold increase in levels from first-dose to steady state, allowing adherence gradients for TFV-DP concentrations in DBS to be estimated based on the number of doses taken per week, over the preceding 6-8 weeks (28). In HIV-negative healthy volunteers receiving TDF/FTC under directly observed therapy, median TFV-DP values of 518, 946, and 1542 fmol/punch were measured in participants randomized to 33% (2-3 doses/week), 67% (4-5 doses/week), and 100% adherence levels (7 doses/week) (30). In another recent large-scale study in PLHIV receiving TDF, the odds of virologic suppression was 76.5 (95% CI 26.6, 220.5) for TFV-DP concentrations >1850 fmol/punch (7 doses administered per week) in comparison <350 fmol/punch (<2 doses per week) (43, 44). In terms of TFV-DP pharmacokinetics, a number of covariates may influence concentrations in both healthy volunteers and persons living with HIV, including race, gender, renal function, and body mass index (BMI) (30, 43), and in those with HIV, concomitant ARV regimen (43). TFV-DP was quantifiable in a small study of 10 participants receiving TAF as part of their ARV treatment regimen, with DBS concentrations ranging between 83-254 fmol/3 mm punch (36). A separate clinical study in HIV-uninfected adults receiving TAF/FTC under directly observed therapy measured median concentrations of 1928 fmol/2x7 mm punches in participants receiving once-daily dosing of this medication (45, 46). The lower TFV-DP concentrations with TAF in DBS compared with TDF dosing suggests that RBCs lack cathepsin A or CES1, and therefore exhibit different cellular pharmacology for TAF versus TDF. Thus, TAF exhibits unique cellular pharmacology versus TDF, characterized by higher cell loading for cells expressing cathepsin A or CES1, lower cellular loading of RBCs, and lower circulating TFV concentrations.

Plasma concentrations of TFV (when administered as TDF) (47-49) and TAF are lower in pregnancy (50). However, data regarding whether corresponding decreases in intracellular levels of TFV-DP may also occur are limited. TFV-DP concentrations in DBS were recently measured in HIV-uninfected pregnant and non-pregnant women receiving TDF/FTC for pre-exposure prophylaxis (PrEP), which revealed ~30% lower TFV-DP concentrations in DBS during pregnancy (51). A separate study to examine TDF/FTC for PrEP in HIV-uninfected pregnant women 16-24 years of age is in development, which will collect DBS samples to measure TFV-DP concentrations in this population (52). In the initial PK component of the study, women will receive TDF/FTC under directly observed therapy. Neither of these studies collected PBMCs, to our knowledge. Thus, TFV-DP concentrations in PBMCs have not been defined in pregnancy. The PK of TAF in plasma among pregnant women living with HIV (WLHIV) was previously examined in IMPAACT P1026s, which found decreased TAF concentrations with 25 mg daily during the second and third trimesters in comparison to postpartum levels, by 64% and 42%, respectively (50). Despite these decreased exposures, 10/11 women were suppressed at the time of delivery, suggesting that intracellular TFV-DP may have remained high enough in immune cells for viral suppression. No significant changes in TAF concentrations between pregnancy and postpartum occurred when TAF 10 mg was co-administered with cobicistat, and 24/27 women were suppressed at delivery. Taken together, these studies suggest that pregnancy alters plasma TFV and TAF disposition, but further investigation is needed to define intracellular concentrations of TFV-DP in DBS and PBMCs among pregnant WLHIV receiving ARV regimens containing TAF.

## 1.2.4 Cabotegravir

Cabotegravir (CAB) is an investigational integrase inhibitor available in two formulations: an oral tablet and a long-acting intramuscular injectable form (CAB LA). The oral tablet was developed for lead-in therapy to establish acute safety and tolerability in individual participants prior to switching to the long-acting formulation (53, 54). In a Phase II study of injectable CAB LA in HIV-uninfected men, 17% of participants had detectable levels of CAB in plasma that persisted 52 weeks after their last injection (55). In a more recent study of women and men receiving injectable CAB, plasma levels of CAB remained above the lower limit of quantification (25 ng/mL LLOQ) in 23% of men and 63% of women at 60 weeks after the final injection and 42% of women and 13% of men at 76 weeks after the final injection. The median estimated time to LLOQ was 66 weeks (range 17 to 182) for women and 42 weeks (range 20 to 134) for men (56).

CAB is highly protein bound in human plasma (>99%). It is a substrate for permeability glycoprotein (P-gp), but because of its high permeability, no alteration in enteral absorption would be expected by co-administration of either P-gp or breast cancer resistance protein (BCRP) inhibitors (57, 58). Unlike some integrase inhibitors, CAB does not require boosting with an additional drug. The primary route of biotransformation is conjugation with glucuronic acid (M1) via UGT1A1. Elimination occurs predominantly in feces via biliary excretion. Renal excretion is minimal, with less than 1% of the dose eliminated in the urine (53, 54, 57-60).

CAB has attributes favorable for both HIV treatment and prevention indications. Currently in Phase II and Phase III clinical trials, it was initially selected for development based on its potential for a high genetic barrier to resistance and a PK profile that allows low-dose, once-daily oral dosing or monthly to quarterly parenteral dosing using a nanosuspension formulation (55). It is anticipated that the first pregnant women exposed to CAB LA will be participants in the HIV Prevention Trials Network (HPTN) 084 study (NCT03164564) entitled “A Phase III double blind safety and efficacy study of Long-Acting Cabotegravir compared to daily oral TDF/FTC for pre-exposure prophylaxis in HIV-uninfected women”. This study will enroll HIV uninfected women at risk of being infected with HIV and randomize them to receive treatment with either CAB LA injections or oral TDF/FTC. While participants in this study are required to use contraception, study investigators expect that several hundred of the 3200 participants will become pregnant during the course of the study. Once pregnancy is identified, participants will be unblinded, and those in the CAB LA injection arm of the study will stop receiving injections for the duration of pregnancy and while lactating after delivery. These participants will receive oral TDF/FTC while injections are being held and may resume CAB LA injections once they have delivered and ceased to breast feed. Pregnant women may also be exposed to injectable CAB in IMPAACT 2017, an open-label Phase I/II study of injectable CAB and rilpivirine (RPV) in HIV-infected children and adolescents. IMPAACT 2017 participants who become pregnant will also stop receiving CAB and RPV injections.

Component 2 Arm 2.1 of IMPAACT 2026 has been developed in collaboration with the HPTN 084 and IMPAACT 2017 Protocol Teams to study washout PK of CAB LA during pregnancy and postpartum and placental and breast milk transfer of CAB LA from mother to fetus/infant in pregnant and postpartum mothers and their infants from HPTN 084 and IMPAACT 2017. Data describing the washout PK of previously injected CAB LA during pregnancy and breastfeeding will provide the initial data needed before studies of CAB LA injections in pregnant/lactating women can be initiated.

Information on HPTN 084 can be found at:  
<https://www.hptn.org/research/studies/hptn084>.

Information on IMPAACT 2017 can be found at:  
<https://impaactnetwork.org/studies/IMPAACT2017.asp>

### 1.3 First-line TB Treatment in Combination with ARVs

TB and HIV co-infection is common in Africa and requires treatment for both diseases, including during pregnancy. In general, the World Health Organization (WHO) recommended first-line TB treatment drugs as safe for use in pregnancy, with the exception of streptomycin due to possible ototoxicity in the fetus (61). However, the Centers for Disease Control and Prevention (CDC) does not recommend the use of pyrazinamide (PZA) in pregnancy due to lack of safety data in humans (62). Currently PK data of first-line TB drugs in pregnant women are limited, with even less data available in HIV co-infection where there is co-administration with ARVs.

Rifampin (RIF) is a critical component of the TB regimen that substantially reduces the risk of relapse after completing TB treatment. RIF is a potent inducer of CYP enzymes and has significant drug interactions with NNRTIs and PIs. Interactions with newer drug families, such as INSTIs, have also been described (63) and as INSTIs are increasingly deemed the preferable choice in ARV regimens, availability of sufficient PK data in the subpopulation of TB-infected pregnant women is extremely important.

Following WHO 2016 guidelines (64) recommending DTG as first-line INSTI-based ARV treatment, several low-income countries have switched to a DTG-based FDC tablet as first-line ARV treatment, including in second or third trimester of pregnancy and with concomitant TB treatment. DTG is known to interact with RIF leading to lower DTG concentration, however these interactions can be overcome by double dosing DTG during RIF co-administration (65). Results from the INSPIRING study show that DTG when administered at 50 mg twice-daily with dual NRTIs, was effective and well-tolerated in HIV/TB co-infected non-pregnant adults receiving RIF-based TB therapy (66). The safety and efficacy of DTG combined with TB treatment in pregnancy, where reduced DTG exposures have been reported in the absence of TB co-treatment, have not yet been investigated.

Important DDIs have also been reported between RIF and PIs. Lopinavir (LPV) metabolism is significantly increased by RIF, and the recommendation is to either double the lopinavir/ritonavir (LPV/r) dose or give additional ritonavir (RTV) when LPV/r and RIF are administered together (63). The standard approach at IMPAACT network African sites is to double the dose of LPV/r in pregnant women on RIF-based TB therapy, as this strategy is known to cause less gastrointestinal side-effects (67). However, these could be aggravated by pregnancy, and safety and efficacy of this strategy in pregnancy has not been described.

Darunavir (DRV) is recommended as a first-line PI-based ARV treatment in high income settings (68), but generally used as third-line ARV only in cases with NNRTI and PI resistance in low income countries. DRV exposure is reduced in pregnancy (69) and the co-administration of DRV and RIF is not recommended (64). However, when no alternative ARV regimens are available, patients on third-line ARV regimens that develop TB infection will have no alternative other than to remain on their current DRV-containing regimen with co-administration of RIF. As the population on third-line ARV treatment will grow over time, it is important to study the DDIs between DRV and TB treatment in pregnancy, as to inform the need to increase DRV dosing during pregnancy.

Rifabutin (RFB), when available, is used as an alternative to RIF in cases where RIF-based TB treatment is prohibited due to interactions with other medications, such as atazanavir (ATV), etravirine (ETR) and standard dose raltegravir (RAL). RFB has shown a much more favorable interaction profile compared to RIF (70). RFB was assigned to pregnancy category B by the FDA and safety and PK data in pregnancy are unavailable (71). The opportunistic design of IMPAACT 2026 will provide an opportunity to study these combinations.

Isoniazid (INH) is used in pregnancy to treat active TB infection as well as latent TB infection in both HIV infected and uninfected women. No adjustment in ARV dosing is required when INH is co-administered according to current WHO guidelines (64). IMAACT P1078, a Phase IV Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Safety of Immediate (Antepartum-initiated) Versus Deferred (Postpartum-initiated) Isoniazid Preventive Therapy among HIV-Infected Women in High TB Incidence Settings presented data at CROI 2018 (72), showing that INH during pregnancy was likely safe for the mother but associated with a higher risk of adverse pregnancy outcomes such as stillbirth and low birth weight. After adjusting for the effect of body size (with allometry) and NAT2 genotype, PK analysis showed that INH clearance was increased by 26% in pregnancy compared to postpartum. 88% of the 815 women were on efavirenz (EFV), and 10% on nevirapine (NVP), and no significant difference in INH clearance was found between these 2 groups (73). Only a small minority (n=17) was co-treated with LPV and no separate PK data were published from this sub-cohort. Another study in non-pregnant participants described a 29% significant decrease in isoniazid exposure (AUC) when co-administered with efavirenz (EFV) (74). The consequence of such a reduction is unknown and the mechanism of action is unclear, however potential mechanisms of action may be through INH that can inhibit cytochrome P450 3A4 (CYP3A4), which also metabolizes EFV and LPV. In a small PK study the administration of INH alone did not lead to higher LPV concentrations in non-pregnant individuals (75). The co-administration of INH and LPV in pregnancy has not yet been adequately studied.

Ethambutol (EMB) is a bacteriostatic drug with low potency, but which targets all bacterial populations and is used in combination therapy to prevent or delay the emergence of resistant strains. PZA is weakly bactericidal but has potent sterilizing activity, and therefore important to avert relapse. Both drugs are not known for interactions with ARVs, but no PK or efficacy data in pregnancy with co-administration of ARVs are available.

The fluoroquinolone moxifloxacin (MFX) has been used as part of second-line TB drug regimens and as an alternative liver friendly TB treatment drug in cases where hepatotoxicity prohibits the use of standard first-line TB treatment drugs. While the fluoroquinolones are not generally preferred TB treatment agents in pregnancy, individual patient factors might still necessitate its use. MFX exposure has been described to be decreased by co-administration of EFV-based ARV and, to a lesser extent, RIF (76). The clinical relevance of the low MFX concentrations for TB treatment outcomes and the need for MFX dose adjustment in the presence of RIF and EFV co-treatment need further investigation, especially in pregnancy.

## **1.4 Second-Line and Newly-Developed TB Drugs with and without ARVs**

In 2016, the WHO assessed new evidence from a meta-analysis of an individual patient database to determine relative contributions of individual TB medicines to treatment outcomes in patients with rifampicin-resistant (RR) or multidrug-resistant (MDR) TB. As a result, TB medicines have been regrouped into three categories (A – C) and ranked based on the latest evidence of effectiveness and safety. Bedaquiline (BDQ), clofazimine (CFZ) and linezolid (LZD) are now

recommended as core second-line TB drugs and fluoroquinolones remain essential in treatment regimens for RR/MDR-TB (77). While treatment during pregnancy was not specifically addressed in this latest communication, the existing 2016 WHO treatment guidelines specifically recommend that pregnant women with RR/MDR-TB are offered individualized regimens which can allow inclusion of four or more effective drugs with no known teratogenic properties (78). There is increasing emphasis on improving access to newer drugs such as BDQ and delamanid (DLM) for people in high-burden programmatic settings, including HIV-infected individuals and special populations such as children, adolescents and pregnant women (79). However, data on the safety and pharmacokinetics of most second-line TB drugs during pregnancy and postpartum remain severely limited. Indeed, “pharmacokinetic studies to determine the optimal TB drug dosing and safety (especially in pregnancy)” was highlighted as one of the MDR-TB research priorities by the Guidelines Development Group in 2015 (80).

A paucity of data also exists for potential DDIs between second-line TB drugs and ARVs, particularly in pregnancy. While there appear to be no significant drug-drug interactions between LZD or DLM and ARVs, CFZ, a weak inhibitor of CYP3A4, may potentially increase PI concentrations (81) and BDQ has a number of important DDIs with ARVs used in first and second-line ARV regimens (82).

IMPAACT 2026 will study the PK and safety during pregnancy and postpartum of prioritized core second-line TB drugs, particularly new and repurposed drugs (i.e. BDQ, DLM, LZD, CFZ and fluoroquinolones) and their use in combination with ARVs (where relevant).

#### Safety

Reports of treatment safety and outcomes with new or repurposed TB drugs (BDQ, DLM, LZD and CFZ) in pregnancy are extremely scarce. While CFZ is known to cross the placenta, it has not yet been associated with teratogenic effects in animals or humans (83) although, Holdiness (in 1989) described 3 neonatal deaths among 13 pregnant women exposed to CFZ (association unclear) (84). Only one case report has been published on safety of a drug regimen including LZD and BDQ, but exposure was limited to 3 weeks in the late third trimester of pregnancy, in a woman treated for extensively drug-resistant TB (XDR-TB); no fetal toxicities were noted two years after delivery (85). To date, there are no published reports of women receiving DLM during pregnancy. In non-pregnant adults, use of BDQ, DLM, CFZ and MFX has been associated with prolongation of the QT interval (86) and LZD commonly causes peripheral neuropathy and bone marrow suppression (87). BDQ has also been associated with an increased risk of hepatitis (88).

#### Pharmacokinetics

One recent (2017) case report of a woman receiving MFX and LZD within a multidrug regimen for MDR-TB during the second and third trimesters of pregnancy and postpartum found a decreased exposure of LZD (at 300mg twice daily) and MFX (at 400mg once daily) during pregnancy compared with postpartum measurements, but with a trend towards increased exposure of both drugs from the second to the third trimesters of pregnancy (89). The optimal effective dose of LZD for MDR-TB has yet to be established in non-pregnant adults (90) and while plasma concentrations appear to be maintained at steady state following oral dosing of 600 mg every 12 hours in healthy volunteers (91), the most commonly used dosing strategy in adults is to start with 600 mg once daily and reduce to 300 mg should toxicity occur. PK data on CFZ are based on studies among patients treated for leprosy, in whom the mean half-life of the drug was approximately 25 days (91). The mean terminal elimination half-life of BDQ and the *N*-monodesmethyl metabolite (M2) among healthy, non-pregnant adults is approximately 5.5 months(92). This likely reflects slow release of BDQ and M2 from peripheral tissues and raises particular concern regarding prolonged fetal exposure to the drug and metabolites in utero and

while breastfeeding. Recently published PK data from studies on rats indicated that DLM radioactivity permeated the placental blood barrier (93) and further PK studies in non-pregnant humans indicate that DLM metabolites are present in much higher concentrations than in rats (94), which may have implications for fetal exposure to DLM.

## 1.5 Breast Milk Transfer of ARV and TB Drugs

Transfer of drugs from lactating mothers to their infants via breast milk depends on maternal, drug and infant factors. The amount of drug in breast milk is determined by the concentration of drug in maternal plasma and by multiple drug characteristics, including degree of protein binding, lipophilicity or hydrophilicity, and ionization, that determine the extent of drug transfer from plasma to breast milk (95). The amount of drug ingested by the infant will depend on breast milk drug concentration and the amount of breast milk consumed by the infant. The infant plasma concentration that will result from the amount of drug ingested via breast milk will depend on the kinetics of drug disposition in the infant, including the rate and extent of drug absorption, pattern of drug distribution and the kinetics of drug metabolism and elimination.

There is a paucity of PK data describing the kinetics of the transfer of first- and second-line TB drugs and antiretrovirals from the breastfeeding mother to her infant via breast milk. Information on breast milk transfer of TB drugs is collated on LactMed, the National Library of Medicine's searchable database of drugs to which breastfeeding mothers may be exposed (96).

For first-line TB drugs, there are only a few case reports published prior to the availability of newer PK assays (97). Vorherr measured breast milk RIF concentration to be 10-30 mg/L, which was 0.05% of the ingested dose of 600 mg (96, 98). EMB in breast milk is only described in 2 personal communications where concentrations were 1.4 and 4.6 mg/L, the latter similar to the maternal plasma concentration (99). PZA breast milk transfer has only been described in 1 case, showing a peak milk level of 1.5 mg/L 3 hours after a 1 gram dose (100). Three studies described INH in breast milk and measured concentrations between 1.7 to 16.6 mg/L, achieving peak concentrations in plasma and breast milk at 2-3 hours after ingestion (101-103). More recently, a paper described breast milk INH peak concentrations of 2-6.7 mg/L after 1 hour, with a very low calculated relative infant dose of 1.2% of the weight adjusted maternal dose (104). A population PK modelling study estimated RIF and EMB breast milk exposure to be as low as 3.7% and 0.3% of the weight adjusted maternal dose when mothers received WHO recommended dosing (105). Although only very low transfer rates were found, for which the concentrations were much lower than the recommended therapeutic dose of the respective drug, the impact of this on the infant, specifically within the setting of HIV exposure or co-infection, has not yet been described.

For second-line TB treatment drugs, the use of fluoroquinolones is considered acceptable during breastfeeding, but information on LZD and CFZ is sparse and for BDQ and DLM not available. Limited data from two single case reports indicated that LZD is excreted into breast milk with peak concentrations between 9.6-18.7 mg/L, but that serum levels of LZD of a nursing infant are trivial and that the maximum dose to which the infant is exposed is much less than the standard infant dose (106, 107). One study described CFZ breast milk concentrations of 0.8-1.7 mg/L (108). Exposure to CFZ in utero and through maternal milk results in skin discoloration in the infant. However, this appears to be reversible on discontinuation of the drug, and no other permanent toxicity has been reported (71). The FDA-approved package insert for BDQ (71) reports findings from rat studies that have shown that concentrations of BDQ in breast milk were 6 to 12-fold higher than the maximum concentrations observed in maternal plasma. It is still not known whether BDQ or its metabolites are excreted in human milk, but the potential adverse consequences of BDQ exposure in breastfed infants is cause for potential concern. According to

the European Medical Association (EMA) product information on DLM, available PK data in animals have shown excretion of DLM and/or its metabolites in breast milk (109), but no further data have been published to date.

Studies describing the kinetics of ARV transfer from mother to infant via breast milk are mostly limited to NRTIs and NNRTIs, with some sparse data for LPV/r (113, 114). Breast milk transfer of many other HIV drugs, including ATV/r and darunavir/ritonavir (DRV/r), have not been studied, as until recently these drugs have had limited availability in resource limited settings where breast feeding is standard for infants of WLHIV. The PI's LPV/r, ATV/r and DRV/r are becoming increasingly available in resource-limited settings, making study of the breast milk transfer of these drugs both feasible and of increasing importance.

Understanding the kinetics of breast milk transfer of TB treatment drugs and ARV's from mother to nursing infant, including an evaluation of infant drug exposure resulting from drug provided by breast milk, is necessary to inform safe maternal drug treatment and breastfeeding practices. Components 2, 3, 4 and 5 of this study are designed to fill in the existing knowledge gaps quickly and efficiently.

## 1.6 Pharmacogenetics

Considerable variability exists in the pharmacokinetics of ARVs in both adults and children. In addition to the changes in drug disposition due to pregnancy, variations in genes that affect drug transport and metabolism creates variability in ARV exposure. The commonly used non-nucleosides all exhibit genetic polymorphisms that impact drug metabolism. CYP 2B6 is responsible for a significant portion of NVP and EFV metabolism and the CYP 2B6 TT genotype at position 516 is associated with impaired metabolism of CYP2B6 substrates (110, 111). This genotype has been reported to be more common in African-Americans (20%) than in European-Americans (3%). The CYP 2B6 516T>T is associated with more than double the EFV AUC in adults (112) and similar increases were observed by Saitoh et al in children (111). More recently, other CYP 2B6 genetic variations have been identified with functional increases and decreases in EFV metabolism (113) and population modelling studies have suggested that polymorphisms 516G>T and 983T>C should both be taken in account with respect to pediatric dosing (114). Similar influence could be expected in adults and implications in pregnancy need to be studied.

There are also potential pharmacogenomic influences on PI absorption and metabolism. Although currently available PIs are pharmacologically boosted by the CYP3A inhibitor, RTV, making patients on RTV-boosted PIs phenotypically poor metabolizers, pharmacogenomic influences on PI exposure still exist. Genetic variants in ORM1 (ORM1\*F1, ORM1\*F2 and ORM1\*S resulting from A to G transition at codons for aa position 20 in exon 1 and 156 in exon 5), SLCO1B1 (rs4149056 and rs4149032), CYP3A5 and pregnane X receptor (PXR) (rs2472677) have been identified to alter LPV or ATV pharmacokinetics (115-118).

Rifampin concentrations have also been shown to be impacted by SLCO1B1 (rs4149032) polymorphism in both Americans (119) and South Africans (120). In turn the altered RIF concentration can influence the known impact of RIF on EFV clearance.

Isoniazid is metabolized by N-acetyl transferase 2 (NAT2), and NAT2 loss-of-function polymorphisms are associated with increased plasma isoniazid exposure. Thus, NAT2 genotype may also contribute to increased plasma efavirenz exposure with antituberculosis therapy, as seen in HIV-infected South African pregnant women with slow NAT2 genotypes, who demonstrated elevated efavirenz concentrations during treatment with isoniazid (121).

In the STRIDE study, slow metabolizer CYP2B6 and NAT2 genotypes were each associated with increased plasma efavirenz concentrations during antituberculosis therapy. Concentrations were greater on therapy than off therapy in 58% with CYP2B6 and 93% with NAT2 slow metabolizer genotypes. Individuals with slow metabolizer genotypes in both genes had markedly elevated concentrations (122).

The identification of genetic influences on the pharmacokinetics of ARVs, TB drugs and the combination thereof is rapidly increasing; however, the interplay between pharmacogenomics and other key factors such as pregnancy are poorly understood. Interactions between pregnancy and pharmacogenomics on ARV and TB drug PK have been shown to exist and are in need of further investigation. In addition to pharmacokinetic-pregnancy interactions, genetic differences in drug metabolism may also alter toxicity. Hepatotoxicity from TB therapy has been linked to drug metabolizing activity of NAT2 and CYP2E1 (123). More recently elevation of liver enzymes has been linked to the drug transporter multi-drug resistance 1 (MDR1) (also known as p-glycoprotein) (124) .

Among mothers in IMPAACT 2026, and infants participating in washout PK and/or breast milk transfer PK sampling, informed consent will be sought for collection and testing of specimens to determine common single nucleotide polymorphisms (SNPs) associated with drug transporters and drug metabolizing enzymes. These assays will allow analyses of the role pharmacogenomic influences may play on ARV and TB drug disposition during pregnancy. In addition, having pharmacogenomic information collected in IMPAACT 2026 participants may help expand the mechanistic understanding of extreme drug exposures or response during pregnancy.

## 1.7 Rationale

IMPAACT P1026s, the predecessor of this study, was first approved in 2003. P1026s enrolled over 1000 pregnant/postpartum women, studied the PK of more than 25 HIV and TB drugs in these women and published 27 manuscripts presenting these data. P1026s data was cited in 32% of the 76 perinatal pharmacology studies in the 2017 version of the United States (US) Department of Health and Human Services (DHHS) Perinatal HIV Guidelines and in 63% of the 27 drug sections contained in these guidelines. Data from the P1026s elvitegravir-cobicistat arm was used as the basis for the 2018 revision of the labels for cobicistat and the cobicistat-containing fixed dose products Stribild, Genvoya, Prezcoibix, Eyotaz, and Symtuza to say that these products are “not recommended for use during pregnancy because of substantially lower exposures of cobicistat and elvitegravir during pregnancy” (125).

Pregnant women continue to be excluded from prelicensure ARV drug development programs, so antiretroviral drugs are approved for use in the absence of pregnancy specific pharmacokinetic and safety data and the need for a study like IMPAACT P1026s continues. Changes in the HIV and TB treatment landscape, in addition to the need to make updates to the protocol to meet current IMPAACT Network standards for protocol documents, data collection, regulatory compliance, and quality assurance, necessitate a new protocol to replace P1026s to continue this critical research. IMPAACT 2026 is an opportunistic study of ARV and TB drugs which are being used as part of clinical care in pregnant and postpartum women but for which there are insufficient or no pregnancy-specific pharmacokinetic or safety data.



IMPAACT 2026 will provide the following:

- The first data describing plasma PK during pregnancy of bicitgravir and doravirine, the newest ARVs, and the first data describing intracellular TFV-DP with use of TAF during pregnancy
- The first data describing washout PK data during pregnancy and postpartum after long-acting injection of CAB
- Critical pregnancy ARV and TB drug PK data for women receiving treatment with first- and second-line TB treatment drugs during pregnancy
- The first data describing the kinetics of mother to infant breast milk drug transfer for several ARVs and TB treatment drugs

The IMPAACT Network and its stakeholders encourages the use of IMPAACT 2026 data in support of modifications of FDA drug labels regarding recommendations for use of a drug during pregnancy. While drug labels should include data and recommendations about use and dosing in pregnancy, pregnant women are excluded from the prelicensing drug development programs for ARVs. As a result, no human PK or safety data relevant to pregnancy are included in initial labels for ARVs. IMPAACT 2026 will continue to provide a primary source of PK data for ARVs in pregnancy.

ARV drug pharmacology in neonates is different from that in older infants and children due to immaturity and the physiologic changes experienced by the neonate during the adaptation to the extrauterine environment in the first weeks of life. ARV drugs may be used in the neonate to prevent or treat HIV infection. Clinical trials studying the neonatal elimination of ARV drugs acquired across the placenta after maternal dosing during pregnancy are critical first steps in understanding the pharmacology of ARV drugs in neonates and establishing safe and effective neonatal dosing regimens. Washout pharmacokinetic data from P1026s infants born to mothers receiving ARVs under study facilitated development of Phase I studies of several ARVs in newborns and infants, including maraviroc and dolutegravir. IMPAACT 2026 will continue to provide initial washout PK data to characterize drug elimination in infants who have received the ARV in utero and to inform the design of further studies including initial dose finding and PK/pharmacodynamic studies in newborns.

## **2 OBJECTIVES**

### **2.1 Primary Objectives**

The primary objectives of this study are to:

- 2.1.1 Component 1: Describe the PK parameters during pregnancy of selected ARV drugs administered to WLHIV who are not receiving TB drugs, and to compare these parameters to (a) historical PK data from non-pregnant women and (b) each participant's own postpartum PK data.
- 2.1.2 Component 2: Describe the kinetics of (a) placental and breast milk transfer of CAB LA from mother to fetus/infant and (b) infant elimination of CAB LA acquired across the placenta after maternal dosing during pregnancy.

- 2.1.3 Component 3: Describe the PK parameters during pregnancy and postpartum of selected ARV drugs and first-line TB treatment drugs co-administered to WLHIV.
- 2.1.4 Component 4: Describe the PK parameters during pregnancy and postpartum of second-line TB treatment drugs administered to WLHIV and HIV-uninfected women.
- 2.1.5 Component 5: Describe the kinetics of drug transfer of selected ARVs from mother to infant via breast milk.

## 2.2 Secondary Objectives

The secondary objectives of this study are to:

- 2.2.1 All Components: Describe maternal and infant safety and clinical outcomes.
- 2.2.2 Components 1, 3 and 4: Compare drug concentrations in plasma from cord blood with concentrations in maternal plasma at delivery for selected ARV and/or TB treatment drugs.
- 2.2.3 Components 1, 3 and 4: Describe the neonatal elimination of selected ARV and/or TB treatment drugs acquired across the placenta after maternal dosing during pregnancy.
- 2.2.4 Components 3 and 4: To describe the kinetics of drug transfer of selected ARVs and/or TB treatment drugs from mother to infant via breast milk.
- 2.2.5 Component 4: Describe the PK parameters of selected ARVs when co-administered with selected second-line TB treatment drugs to WLHIV during pregnancy and postpartum.

## 2.3 Other Objectives

The other objectives of this study are to:

- 2.3.1 Assess plasma protein binding of highly bound ARVs and/or TB treatment drugs during pregnancy and postpartum.
- 2.3.2 Explore genetic sources for variability in drug exposure in pregnant women, postpartum women, and infants for selected ARV and/or TB treatment drugs.

## 3 STUDY DESIGN

This is a Phase IV prospective study to describe the PK of ARV and TB drugs when used alone or in combination during pregnancy or postpartum, among 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 [Figure 1](#) for an overview of the study design and to [Table 1](#) in [Section 5](#) for the drugs being evaluated in each arm. To be eligible for the study, women must have received at least one of the drugs or drug combinations being evaluated (from a non-study source) and must meet the relevant criteria specified in [Section 4](#). Infants born to women enrolled in all Components will also be enrolled. The design of each component is described in [Sections 3.1-3.5](#).

Note: Refer to [Section 9.3](#) for further discussion of enrollment limits and to [Section 9.6.1](#) for the definition of evaluable applicable to each component. Opening of any individual study arm may be delayed until clinical use of the regimen being studied is common enough at participating sites to support adequate enrollment in the arm.

### 3.1 Component 1: Pregnant WLHIV receiving oral ARVs and no TB drugs, and their infants

Pregnant WLHIV who meet the criteria specified in [Sections 4.1.1 and 4.2](#) will be enrolled in this component during the second (20 0/7 weeks - 26 6/7 weeks gestation) or third (30 0/7 weeks - 37 6/7 weeks gestation) trimester of pregnancy. The infants of these women will be enrolled *in utero*.

Up to 28 women and their infants will be enrolled per arm to achieve a target of 25 in each arm with evaluable third trimester PK data; enrollment of at least 12 women in each arm with evaluable second trimester PK data will also be targeted. Eligible women receiving multiple Component 1 drugs under study may contribute data to multiple Component 1 study arms. Refer to the component-specific maternal Schedule of Evaluations (SoE) in [Appendix I-A](#). Women in this component will be followed through delivery and for 6-12 weeks post-delivery. Infants will be followed through 24 weeks post-birth. Clinical and laboratory evaluations for safety monitoring will be performed throughout maternal follow-up.

For women in Arms 1.1 and 1.2, intensive PK sampling will be performed during the second trimester (for women enrolled in the second trimester), the third trimester (for all women), and 6-12 weeks postpartum (for all women). For women in Arms 1.3, 1.4, and 1.5, sparse PK sampling, including DBS and PBMC processing, will be performed to determine intracellular TAF concentrations during the second trimester (for women enrolled in the second trimester), the third trimester (for all women), and 6-12 weeks postpartum (for all women). For each woman, initial PK sampling should be targeted to be performed within 5 days of enrollment but must be performed no later than 14 days after enrollment. At delivery, samples of maternal and cord blood will be collected for comparison of maternal and fetal plasma PK (Arms 1.1 and 1.2) or intracellular TAF concentrations (Arms 1.3, 1.4, and 1.5). Plasma AAG concentration and protein binding will also be determined for all highly bound ARV drugs. If consent is provided, a DBS sample will be obtained from the first PK sample for pharmacogenetic testing.

For select ARVs (Arms 1.1 and 1.2), ARV plasma drug assays and PK calculations will be performed in real time during pregnancy and results will be reported to participants and their clinical caregivers. The participant and caregiver may decide to modify dosing, and if so, additional PK sampling may be performed. Refer to [Section 10.4.2](#) for further details.

Refer to the infant SoE in [Appendix II-A](#). Infants in this component will be followed for 16-24 weeks after birth. Clinical evaluations will be performed at birth and throughout follow-up. Infants who meet the criteria in [Section 6.10.3](#) will undergo washout PK sampling at birth and 5-9 days after birth. If consent is provided and the infant meets washout PK sampling criteria, a DBS sample will be obtained from the first PK sample for pharmacogenetic testing.

### **3.2 Component 2: Pregnant WLHIV and HIV-uninfected women who received long-acting/extended release ARVs during pregnancy, and their infants**

Pregnant women who meet the criteria specified in [Sections 4.1.2](#) and [4.2](#) will be enrolled in this component after 24 0/7 weeks gestation but prior to delivery. The infants of these women will be enrolled *in utero*.

Up to 28 women will be enrolled per arm to achieve a target of 25 women with evaluable CAB LA delivery PK data, and a target of 25 infants with evaluable infant CAB LA washout PK data.

Refer to the component-specific maternal SoE in [Appendix II-B](#). Women in this component will be followed through delivery. Women who meet the criteria in [Section 6.10.4](#) for breast milk transfer sampling will additionally be followed through 3-5 weeks post-delivery. Clinical and laboratory evaluations for safety monitoring will be performed throughout maternal follow-up.

At delivery, samples of maternal and cord blood will be collected for comparison of maternal and fetal plasma ARV concentrations at birth. Plasma AAG concentration and protein binding will also be determined for all highly bound ARV drugs. If consent/assent is provided, a DBS sample will be obtained from the delivery PK sample for pharmacogenetic testing.

Refer to the component-specific infant SoE in [Appendix II-B](#). Infants in this component will have a birth visit. Infants who meet the criteria in [Section 6.10.3](#) will undergo additional sampling at birth, at 5-9 days and at 12-16 days after birth for washout PK evaluation. Infants who meet the criteria in [Section 6.10.4](#) will undergo additional PK sampling at 3-5 weeks after birth for breast milk transfer evaluation. If consent/assent is provided and the infant meets breast milk transfer PK sampling criteria, a DBS will be stored for pharmacogenetic testing.

### **3.3 Component 3: Pregnant WLHIV receiving ARVs and first-line TB treatment, and their infants**

Pregnant WLHIV who meet the criteria specified in [Sections 4.1.3](#) and [4.2](#) will be enrolled during the second trimester (20 0/7 weeks - 26 6/7 weeks gestation) or third trimester (30 0/7 weeks - 37 6/7 weeks gestation) of pregnancy. The infants of these women will be enrolled *in utero*.

Up to 28 women and their infants will be enrolled per arm to achieve a target of 25 in each arm with evaluable third trimester PK data; enrollment of at least 12 women in each arm with evaluable second trimester PK data will be targeted. Eligible women receiving multiple Component 3 drugs under study may contribute data to multiple Component 3 study arms.

Refer to the component-specific maternal SoE in [Appendix II-A](#). Women in this component will be followed through delivery and for 2-8 weeks postpartum; women enrolled in select arms (Arms 3.2 or 3.3) who meet the criteria in [Section 6.10.4](#) for breast milk transfer sampling will additionally be followed through 16-24 weeks postpartum. Clinical and laboratory evaluations for safety monitoring will be performed throughout maternal follow-up.

Intensive PK sampling for ARV and TB treatment drugs will be performed during the second trimester (for women enrolled during the second trimester), the third trimester (for all women), and 2-8 weeks postpartum (for all women). For each woman, initial PK sampling should be targeted to be performed within 5 days of enrollment, but must be performed no later than 14 days after enrollment. At delivery, samples of maternal and cord blood will be collected for comparison of maternal and fetal plasma PK of ARV and TB treatment drugs if the mother is still

on TB treatment. Women who have completed TB treatment after the entry visit are no longer eligible for intensive PK sampling during study visits but will be followed for clinical outcomes and possible breast milk transfer of remaining eligible drugs. Women in select study arms (Arms 3.2 or 3.3) meeting criteria for evaluation of breast milk transfer will undergo additional visits at 5-9 days post-delivery and 16-24 weeks post-delivery, and samples of plasma and breast milk will be collected for breast milk transfer analysis of both ARV and TB treatment drugs. Plasma AAG concentration and protein binding will also be determined for all highly bound ARV and TB treatment drugs. If consent/assent is provided, a DBS will be stored for pharmacogenetic testing.

For select ARVs (Arms 3.1, 3.2, and 3.3), ARV plasma drug assays and PK calculations will be performed in real time during pregnancy and results will be reported to participants and their clinical caregivers. The participant and caregiver may decide to modify dosing, and if so, additional PK sampling may be performed. Refer to [Section 10.4.2](#) for further details.

Refer to the component-specific infant SoE in [Appendix II-A](#). Infants in this component will be followed for 16-24 weeks after birth. Clinical evaluations will be performed at birth and throughout follow-up. Infants who meet the criteria in [Section 6.10.3](#) will undergo washout PK sampling for ARV and TB treatment drugs at birth and within 5-9 days after birth. Infants enrolled in select arms (Arms 3.2 or 3.3) who meet the criteria in [Section 6.10.4](#) will undergo additional PK sampling for breast milk transfer of ARV and TB treatment drugs at 2-8 weeks and 16-24 weeks after birth. If consent/assent is provided and the infant meets washout PK sampling criteria, a separate DBS sample will be obtained from the first PK sample for pharmacogenetic testing.

### **3.4 Component 4: Pregnant WLHIV and HIV-uninfected women, receiving second-line TB treatment, and their infants**

WLHIV and HIV-uninfected pregnant women who meet the criteria specified in [Sections 4.1.4](#) and [4.2](#) will be enrolled during the second trimester (20 0/7 weeks - 26 6/7 weeks gestation) or third trimester (30 0/7 weeks - 37 6/7 weeks gestation) of pregnancy. The infants of these women will be enrolled *in utero*.

Up to 28 women and their infants will be enrolled per arm to achieve a target of 25 with evaluable third trimester PK data; enrollment of at least 12 women in each arm with evaluable second trimester PK data will be targeted.

Refer to the component-specific maternal SoE in [Appendix I-D](#). Women in this component will be followed through delivery and for 2-8 weeks postpartum; women who meet the criteria in [Section 6.10.4](#) for breast milk transfer sampling will additionally be followed through 16-24 weeks postpartum. Clinical and laboratory evaluations for safety monitoring will be performed throughout maternal follow-up.

Intensive PK sampling for TB treatment drugs will be performed during the second trimester (for women enrolled during the second trimester), the third trimester (for all women), and 2-8 weeks postpartum (for all women). Additionally, intensive PK for ARV drugs will be performed at these same visits for WLHIV also taking ARVs under study specified in [Table 1](#). WLHIV taking other ARV drugs will not undergo intensive PK sampling for those ARVs.

Initial PK sampling should be targeted to be performed within 5 days of enrollment but must be performed no later than 14 days after enrollment. At delivery, samples of maternal and cord blood will be collected for comparison of maternal and fetal plasma PK of TB treatment drugs. Women who completed TB treatment after the entry visit are no longer eligible for intensive PK sampling during study visits but will be followed for clinical outcomes and possible breast milk transfer of remaining eligible drugs. Women meeting criteria for evaluation of breast milk transfer will undergo additional visits at 5-9 days post-delivery and 16-24 weeks post-delivery, and samples of plasma and breast milk will be collected for breast milk transfer analysis of TB treatment drugs. Plasma AAG concentration and protein binding will also be determined for all highly bound TB and ARV drugs. If consent/assent is provided, a DBS sample will be obtained from the first PK sample for pharmacogenetic testing. For WLHIV who are also taking select ARVs ([Table 1](#)), ARV plasma drug assays and PK calculations will be performed in real-time during pregnancy and results will be reported to participants and their clinical caregivers. The participant and caregiver may decide to modify dosing, and if so, additional PK sampling may be performed. Refer to [Section 10.4.2](#) for further details.

Refer to the component-specific infant SoE in [Appendix II-A](#). Infants in this component will be followed for 16-24 weeks after birth. Clinical evaluations will be performed at birth and throughout follow-up. Infants who meet the criteria in [Section 6.10.3](#) will undergo washout PK sampling for TB treatment drugs at birth and 5-9 days after birth. Infants who meet the criteria in [Section 6.10.4](#) will undergo additional PK sampling for breast milk transfer of TB treatment drugs at 2-8 weeks and 16-24 weeks after birth. If consent/assent is provided and the infant meets washout PK sampling criteria, a separate DBS sample will be obtained from the first infant PK sample for pharmacogenetic testing.

### **3.5 Component 5: Postpartum WLHIV breastfeeding while receiving oral ARVs, and their infants**

Breastfeeding mother-infant pairs receiving ARVs who meet the eligibility criteria specified in [Section 4.1.5 and 4.3](#) will be enrolled between 5 – 9 days after delivery.

Up to 15 mother-infant pairs will be enrolled per arm to achieve a target of 15 mother-infant pairs per arm with evaluable PK data at the 2-12 week post-delivery visit. The target is 15 evaluable per arm as data from mother-infant pairs undergoing breast milk transfer PK sampling as part of other components studying the same drugs will be combined with data from Component 5. Eligible women receiving multiple Component 5 drugs under study may contribute data to multiple Component 5 study arms.

Refer to the component-specific maternal and infant SoEs in [Appendix I-E](#) and [Appendix II-C](#), respectively. Women and their infants enrolled in Component 5 arms will be followed for 16-24 weeks post-delivery or until breastfeeding cessation, if cessation is prior to 16-24 weeks post-delivery. Clinical evaluations for safety monitoring will be performed throughout follow-up. Plasma and breast milk samples will be collected at 5-9 days, 2-12 weeks, and 16-24 weeks after delivery.

## 4 STUDY POPULATION

This study will be conducted among pregnant and postpartum WLHIV and HIV-uninfected women receiving ARV and/or TB drugs under study, and their infants. Mothers and infants will be assessed for eligibility per the component-specific criteria specified in [Sections 4.1–4.4](#), and the requirements in [Section 4.5](#) and [4.6](#). The study-specific approach to recruitment, screening, and enrollment is described in [Section 4.7](#). Considerations related to participant retention and withdrawal/termination from the study are provided in [Sections 4.8](#) and [4.9](#), respectively.

### 4.1 Inclusion Criteria

Potential participants must meet all inclusion criteria for at least one component as specified below.

#### 4.1.1 Component 1: Pregnant WLHIV receiving oral ARVs and no TB drugs, and their infants

Potential mother-infant pairs must meet all of the following maternal inclusion criteria to be enrolled in Component 1. There are no fetal or infant inclusion criteria applicable to this component. The infant will be enrolled *in utero*, at the same time as the mother.

- 4.1.1.1 Mother is of legal age or otherwise able to provide independent informed consent as determined by site SOPs and consistent with site IRB/EC policies and procedures, and is willing and able to provide written informed consent for her own and her infant's participation in this study.
- 4.1.1.2 Prior to study entry, HIV status confirmed as HIV infected per [Section 4.5](#).
- 4.1.1.3 At study entry, pregnant and in one of the following two enrollment windows based on best available obstetrical estimate of gestational age:
  - Second trimester: gestational age of 20 0/7 to 26 6/7 weeks
  - Third trimester: gestational age of 30 0/7 to 37 6/7 weeks
- 4.1.1.4 At study entry, receiving at least one of the following oral ARV drugs or drug combinations, based on maternal report and available medical records:

<b>Arm 1.1</b>	Bictegravir (BIC) 50 mg q.d.
<b>Arm 1.2</b>	Doravirine (DOR) 100 mg q.d.
<b>Arm 1.3</b>	Tenofovir alafenamide (TAF) - 10 mg q.d. boosted with cobicistat
<b>Arm 1.4</b>	TAF 25 mg q.d. without boosting
<b>Arm 1.5</b>	TAF 25 mg q.d. boosted with cobicistat or ritonavir
- 4.1.1.5 At study entry, planning to continue the current ARV regimen through at least 12 weeks post-delivery, based on maternal report and available medical records.
- 4.1.1.6 At study entry, has been receiving the drug or drug combination under study at the required dose for at least two weeks, based on maternal report and available medical records.

- 4.1.1.7 At study entry, assessed by study staff as having no identified barriers to completing initial PK sampling within 20 0/7 – 26 6/7 weeks gestation (second trimester) or 30 0/7 to 37 6/7 weeks gestation (third trimester) and within 14 days of enrollment.
- 4.1.1.8 At study entry, if receiving a generic formulation of the drug or drug combination under study, approval of the formulation per [Section 5.1](#).
- 4.1.1.9 At study entry, not receiving any TB drugs (for either prophylaxis or treatment), based on maternal report and available medical records.

#### 4.1.2 **Component 2: Pregnant WLHIV and HIV-uninfected women who received long-acting/extended release ARVs during pregnancy, and their infants**

Potential mother-infant pairs must meet all of the following maternal inclusion criteria to be enrolled in Component 2. There are no fetal or infant inclusion criteria applicable to this component. The infant will be enrolled *in utero*, at the same time as the mother.

- 4.1.2.1 *If of legal age or otherwise able to provide independent informed consent as determined by site SOPs and consistent with site IRB/EC policies and procedures:* Willing and able to provide written informed consent for her own and her infant’s participation in this study.  
  
*If not of legal age or otherwise unable to provide independent informed consent as determined by site SOPs and consistent with site IRB/EC policies and procedures:* Parent/guardian or other legally authorized representative of the mother and her infant is willing and able to provide written informed consent for the mother and her infant’s study participation; in addition, when applicable, the mother is willing and able to provide written assent for her own and her infant’s study participation.
- 4.1.2.2 At study entry, intends to deliver at the study-affiliated clinic or hospital, based on maternal report.
- 4.1.2.3 At study entry, gestational age of at least 24 0/7 weeks based on best available obstetrical estimate of gestational age, and not yet delivered.
- 4.1.2.4 At study entry, has received at least one administration of the following, based on available medical records, during the current pregnancy:

**Arm 2.1** Long-acting injectable formulation of cabotegravir (CAB LA) (any dose)

#### 4.1.3 **Component 3: Pregnant WLHIV receiving ARVs with first-line TB treatment, and their infants**

Potential mother-infant pairs must meet all of the following maternal inclusion criteria to be enrolled in Component 3. There are no fetal or infant inclusion criteria applicable to this component. The infant will be enrolled *in utero*, at the same time as the mother.

- 4.1.3.1 Mother is of legal age or otherwise able to provide independent informed consent as determined by site SOPs and consistent with site IRB/EC policies and procedures,



and is willing and able to provide written informed consent for her own and her infant's participation in this study.

- 4.1.3.2 Prior to study entry, HIV status confirmed as HIV infected per [Section 4.5](#).
- 4.1.3.3 At study entry, pregnant and in one of the following two enrollment windows, based on best available obstetrical estimate of gestational age:
  - Second trimester: gestational age of 20 0/7 to 26 6/7 weeks
  - Third trimester: gestational age of 30 0/7 to 37 6/7 weeks
- 4.1.3.4 At study entry, receiving at least two of the following first-line TB treatment drugs under study AND at least one of the following ARV drugs or drug combinations under study, based on maternal report and available medical records:

First-line TB treatment drugs:

- Isoniazid (INH) 4-6 mg/kg (max 300 mg) q.d.
- Rifampin (RIF) 8-12 mg/kg (max 600 mg) q.d.
- Rifabutin (RFB) 150-300 mg q.d.
- Ethambutol (EMB) 15-20 mg/kg q.d.
- Pyrazinamide (PZA) 20-30 mg/kg q.d.
- Moxifloxacin (MFX) 400 mg or 800mg q.d.

ARVs:

- Arm 3.1** Dolutegravir (DTG) 50 mg b.i.d. when combined with RIF or 50 mg q.d. if RIF is not part of the TB regimen
- Arm 3.2** Atazanavir/ritonavir (ATV/r)  $\geq 300/100$  mg q.d. or Darunavir/ritonavir (DRV/r)  $\geq 600/100$  mg b.i.d.
- Arm 3.3** Lopinavir/ritonavir (LPV/r) 800/200 mg b.i.d.

- 4.1.3.5 At study entry, has been receiving the drug combination under study at the required dose for at least two weeks based on maternal report and available medical records.
- 4.1.3.6 At study entry, assessed by study staff as having no identified barriers to completing initial PK sampling within 20 0/7 – 26 6/7 weeks gestation (second trimester) or 30 0/7 to 37 6/7 weeks gestation (third trimester) and within 14 days of enrollment.
- 4.1.3.7 At study entry, if receiving a generic ARV or TB formulation of the drug or drug combination under study, approval of the formulation per [Section 5.1](#).
- 4.1.3.8 At study entry, planning to continue the current ARV regimen through at least 8 weeks post-delivery, based on maternal report and available medical records.

#### 4.1.4 **Component 4 Inclusion Criteria: Pregnant WLHIV and HIV-uninfected women receiving second-line TB treatment, and their infants**

Potential mother-infant pairs must meet all of the following maternal inclusion criteria to be enrolled in Component 4. There are no fetal or infant inclusion criteria applicable to this component. The infant will be enrolled *in utero*, at the same time as the mother.

- 4.1.4.1 Mother is of legal age or otherwise able to provide independent informed consent as determined by site SOPs and consistent with site IRB/EC policies and procedures, and is willing and able to provide written informed consent for her own and her infant's participation in this study.
- 4.1.4.2 Prior to study entry, HIV status confirmed as HIV-infected or HIV-uninfected, per [Section 4.5](#).
- 4.1.4.3 At study entry, pregnant and in one of the following two enrollment windows based on best available obstetrical estimate of gestational age:
  - Second trimester: gestational age of 20 0/7 to 26 6/7 weeks
  - Third trimester: gestational age of 30 0/7 to 37 6/7 weeks
- 4.1.4.4 At study entry, receiving at least one of the following second-line TB treatment drugs under study, based on maternal report and available medical records:
 

**Arm 4.1**      Second-line TB treatment drugs:

  - Levofloxacin (LFX) 750mg – 1000mg q.d.
  - Clofazimine (CFZ) 100mg q.d.
  - Linezolid (LZD) 300mg – 600mg q.d.
  - Bedaquiline (BDQ) 200mg t.i.w.
  - Delamanid (DLM) 100mg b.i.d.
  - Moxifloxacin (MXF) 400mg or 800mg q.d **and** at least one other second-line TB treatment drug under study
- 4.1.4.5 At study entry, has been receiving the drugs under study at the required dose for at least two weeks, based on maternal report and available medical records.
- 4.1.4.6 At study entry, assessed by study staff as having no identified barriers to completing initial PK sampling within 20 0/7 – 26 6/7 weeks gestation (second trimester) or 30 0/7 to 37 6/7 weeks gestation (third trimester) and within 14 days of enrollment.
- 4.1.4.7 At study entry, if receiving a generic formulation of the drug(s) under study, approval of the formulation per [Section 5.1](#).

#### 4.1.5 Component 5: Postpartum WLHIV breastfeeding while receiving oral ARVs, and their infants

Potential mother-infant pairs must meet all of the following inclusion criteria to be enrolled in Component 5.

- 4.1.5.1 Mother is of legal age or otherwise able to provide independent informed consent as determined by site SOPs and consistent with site IRB/EC policies and procedures, and is willing and able to provide written informed consent for her own and her infant's participation in this study.
- 4.1.5.2 Prior to study entry, HIV status confirmed as HIV infected, per [Section 4.5](#).
- 4.1.5.3 At study entry, within 5-9 days post-delivery (inclusive).

- 4.1.5.4 At study entry, breastfeeding mother-infant pair intends to continue exclusive breastfeeding through at least 16 weeks post-delivery.
- 4.1.5.5 At study entry, mother is receiving any of the following oral ARV drugs or drug combinations:
  - Arm 5.1 Atazanavir/ritonavir (ATV/r)
  - Arm 5.2 Darunavir/ritonavir (DRV/r)
  - Arm 5.3 Lopinavir/ritonavir (LPV/r)
- 4.1.5.6 At study entry, mother has been receiving the drug(s) or drug combination(s) under study at the required dose for at least two weeks, based on maternal report and available medical records.
- 4.1.5.7 At study entry, assessed by study staff as having no identified barriers to completing initial PK sampling within the 5-9 days post-delivery PK sampling window.
- 4.1.5.8 At study entry, mother is planning to continue the current ARV regimen through at least 16 weeks post-delivery, based on maternal report and available medical records.
- 4.1.5.9 At study entry, if receiving a generic ARV formulation of the drug or drug combination under study, approval of the formulation per [Section 5.1](#).
- 4.1.5.10 At study entry, infant weighs at least 1000 grams, based on available medical records.
- 4.1.5.11 At study entry, infant does not have any severe congenital malformation or other medical condition not compatible with life or that would interfere with study participation or interpretation, as judged by the site investigator.

## 4.2 Components 1-4 Exclusion Criteria

Potential participants (mother-infant pairs) who meet any of the following criteria will be excluded from this study:

- 4.2.1 At study entry, mother has received within the past 14 days medicines known to interfere with absorption, metabolism, or clearance of the drug or drug combination under study (see [Section 5.4](#)) based on maternal report and available medical records.  
  
*(Note: RIF is permitted for mothers in Components 3 and 4 being evaluated for TB and ARV drug interactions).*
- 4.2.2 At study entry, has a clinical or laboratory finding or condition that, in the opinion of the site investigator, is likely to require a change of the ARV or TB drug under study during the period of study follow-up.
- 4.2.3 **Arms 1.3, 1.4 and 1.5 only:** At study entry, mother has received TDF-based therapy within the past 6 months.

### 4.3 Component 5 Exclusion Criteria

Potential participants (mother-infant pairs) who meet any of the following criteria will be excluded from this Component 5:

- 4.3.1 Mother is currently enrolled in Components 1, 2, 3, or 4.
- 4.3.2 At study entry, the mother or infant has received within the past 14 days medicines known to interfere with absorption, metabolism, or clearance of the drug or drug combination under study based on maternal report and available medical records (See [Section 5.4](#)).
- 4.3.3 At study entry, mother or infant has a clinical or laboratory finding or condition that, in the opinion of the site investigator, is likely to require a change of the drug under study during study follow-up.

### 4.4 Infant Enrollment

Infants in Components 1-4 are enrolled in the study *in utero*, at the same time as maternal enrollment. Infants in Component 5 are enrolled in the study after birth, at the same time as maternal enrollment. Infants must meet certain additional requirements (after enrollment) to undergo PK sampling procedures per [Sections 6.10.3](#) and [6.10.4](#).

### 4.5 Confirmation of Maternal HIV Status

All study-specific samples tested to determine HIV status must be whole blood, serum, or plasma using test methods approved for each site by the IMPAACT Laboratory Center (for National Institute of Allergy and Infectious Diseases (NIAID) sites) or Westat [for National Institute of Child Health and Human Development (NICHD) sites]. All test methods should be FDA-approved, if available. This does not apply to test results obtained from medical records from tests conducted outside of IMPAACT 2026.

#### 4.5.1 Women Presumed not to be Infected with HIV

*For potential participants initially presumed by study site staff to be **HIV-uninfected** based on medical records or participant report:*

A study-specific sample must be collected during the study screening period and tested per the Sample #1 requirements in [Section 4.5.3](#).

- Participants with negative results from this testing will be considered HIV-uninfected at entry.
- Participants with positive test results should be referred to non-study sources of HIV care and treatment as soon as possible and may be considered for entry into the study as HIV-infected, following confirmation of HIV infection per the Sample #1 and Sample #2 requirements as described in [Section 4.5.3](#).

## 4.5.2 Women Presumed to be Living with HIV

*For potential participants initially presumed by study site staff to be living with **HIV** based on medical records or participant report:*

HIV infection must be confirmed based on test results from two samples collected from two separate blood collection tubes with Sample #1 and Sample #2 testing performed per [Section 4.5.3](#). Test results may be obtained from medical records or from testing performed during the study screening period:

- For results obtained from medical records, adequate source documentation, including the date of specimen collection, date of testing, name of test/assay performed, and test result must be available in study records prior to study entry. Requirements related to laboratory operations (e.g., CLIA, GCLP, or VQA) and related to regulatory authority approvals (e.g., FDA) do not apply to results obtained from medical records.
- If adequate source documentation is not available, Sample #1 and/or Sample #2 should be collected during the study screening period and tested in the study site's designated testing laboratory. If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to Clinical Laboratory Improvement Amendments (CLIA)-certified (for US sites) or Good Clinical Laboratory Practices (GCLP) guidelines (for non-US sites) and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in the study site's CLIA-certified (for US sites) or VQA-certified (for non-US sites) laboratory.

Participants with positive results from Sample #1 and Sample #2 meeting the requirements listed above will be considered HIV-infected at entry.

## 4.5.3 HIV Testing Requirements

Sample #1 may be tested using any of the following:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes
  - *For potential participants presumed HIV uninfected:* HIV-infection may be ruled out for purposes of eligibility determination based on a negative result from at least one FDA-approved HIV rapid test (in this context, it is not necessary to perform two rapid tests).
  - *For potential participants presumed HIV-infected:* Two rapid tests should be performed.
- One enzyme immunoassay (EIA) or Western Blot OR immunofluorescence assay OR chemiluminescence assay
- One HIV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR)
- One quantitative HIV ribonucleic acid (RNA) PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid test

Sample #2 may be tested using any of the following:

- Rapid antibody test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope

- One EIA or Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid test

In the event that the second test does not confirm an initial positive result, the Core Protocol Team should be consulted for guidance on next steps to clarify the participant's HIV status. Enrollment should not occur until HIV status is clarified in consultation with the team. Pending confirmatory testing, ARV prophylaxis and/or treatment should be managed consistent with local standards of care.

#### **4.6 Co-Enrollment Considerations**

Participants in HPTN 084 and IMPAACT 2017 may be co-enrolled in Arm 2.1 of this study with no prior approval required. Participants enrolled in studies of the Pediatric HIV/AIDS Cohort Study (PHACS) Network may be co-enrolled in any component with no prior approval required. Otherwise, co-enrollment in this study and other studies requires approval in advance from both Protocol Teams. Requests for such approval should be emailed to the Core Protocol Team.

#### **4.7 Recruitment, Screening, and Enrollment Process**

Recruitment methods for this study 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.

Upon identification of a potentially eligible participant, study staff will provide information about the study to the potential participant and her parent/guardian (as applicable). Each potential participant who expresses interest in learning more about the study will be provided additional information, education and counseling as part of the study informed consent and assent processes. The process will include detailed review of the study informed consent and assent forms (as applicable), time to address any questions or concerns the potential participant and her parent/guardian (if applicable) may have, and an assessment of understanding, before proceeding to informed consent/assent decisions. 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 visits may take place within the specified windows. Informed consent and assent processes will be fully documented, consistent with the NIAID DAIDS policies referenced in [Section 11.2](#). Refer to [Section 13.3](#) for further information on informed consent procedures for this study.

Eligibility screening will be initiated after written informed consent and assent (as applicable) is provided. Screening evaluations must be completed prior to enrollment; re-screening is permitted. Screening evaluations may be performed up to and on the day of enrollment; however, all required screening outcomes, including confirmation of HIV infection status, must be available prior to enrollment.

Each site must establish SOPs for eligibility determination that describe where and when screening procedures will be performed; roles and responsibilities for performing the required procedures; roles and responsibilities for assessing and confirming eligibility; and procedures for documenting the process, taking into consideration the required timing of entry.

Prior to enrollment, and after informed consent (or assent, if applicable) is obtained, sites will assign a participant identification number (PID) to the participant and a PID to her infant/fetus. The IMPAACT Data Management Center (DMC) Subject Enrollment System (SES) will be used to enroll participants in this study. For mothers and infants found to be eligible, enrollment will occur upon successful entry of required eligibility data into the SES. The mother must be enrolled first, followed immediately by the infant. In Components 1 – 4, enrollment of the mother and infant occurs while the infant is *in utero*. In Component 5, enrollment of the mother and infant occurs after the infant is born. Successful entry into the SES will generate a study identification number (SID), for each enrolled participant. Refer to [Section 9.5](#) for more information on monitoring participant accrual in this study.

Mothers who are taking two or more of the drug or drug combinations under study may undergo PK sampling for each drug or combination and thereby contribute to the targeted sample size for all applicable study arms, as long as eligibility criteria are met and blood draw maximums will not be exceeded by doing so (see [Section 6.12](#)). Information entered in the SES will identify each drug under study the mother is receiving. After completing scheduled visits and procedures for a given study arm, if a mother becomes pregnant again, she may be re-enrolled in the study if she meets eligibility criteria for a different arm.

#### **4.8 Participant Retention**

Once a participant is enrolled in this study, study staff will make every effort to retain her for the protocol-specified duration of follow-up, thereby maximizing evaluability and statistical power and minimizing potential biases associated with loss to follow-up. Study sites are responsible for developing and implementing local procedures to reach this goal. Refer to [Section 9.5](#) for more information on monitoring participant retention in this study.

#### **4.9 Participant Withdrawal or Termination from the Study**

Regardless of the participant retention procedures referenced above, participants may voluntarily withdraw from the study. Participants may also be terminated from the study by the site investigator or designee under the following circumstances:

- Participant re-locates away from the study site or is otherwise determined to be lost-to-follow-up
- Investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the participant, after consultation with the Core Protocol Team
- Participant only being evaluated for breast milk transfer PK is no longer breastfeeding her infant or no longer meets breast milk transfer PK requirements per [Section 6.10.4](#).
- Participant fails to comply with study requirements so as to cause harm to self or seriously interfere with the validity of the study results
- The study is stopped or canceled by the sponsors, government or regulatory authorities, or site IRBs/ECs.

- Participant is unable to complete initial PK evaluation within protocol-specified timeframe

Should the consenting parent or guardian of an enrolled underage maternal participant or an enrolled infant die or no longer be available for any reason, no further study-specific evaluations should be performed until informed consent for continued study participation is obtained from an authorized guardian, as defined locally. Study sites may continue to provide care for the infant as needed and appropriate (outside of the study) consistent with the local standard of care but no study-specific procedures may be performed. If an authorized guardian cannot be identified, or if the authorized guardian does not consent to continued infant study participation, the infant must be terminated from the study. Refer to [Section 13](#) for further guidance on guardian consent for study participation.

For any participant who withdraws or is terminated from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal or termination in detail and enter the reason into the appropriate eCRF. No final evaluations are required in the case of early termination or withdrawal. If the circumstances that led to a participant’s withdrawal or termination change (e.g., he or she returns to the study site area after having re-located previously), the site investigator or designee should contact the Core Protocol Team to discuss options for resumption of follow-up.

## 5 DRUGS UNDER STUDY

The drugs and drug combinations being evaluated in this study are referred to as ‘drugs under study’ and are listed by component and arm in [Table 1](#). No ARVs or TB treatment drugs are supplied as part of this study. All drugs under study are provided by non-study sources (e.g. clinical care providers or another research study).

**Table 1. Components, Arms and Drugs under Study**

Component	Arm	Drug or Drug Combination under Study
<b>Component 1</b> Pregnant WLHIV receiving oral ARVs and no TB drugs, and their infants	1.1	Bictegravir (BIC) 50 mg q.d.
	1.2	Doravirine (DOR) 100 mg q.d.
	1.3	Tenofovir (TAF) 10 mg q.d. boosted with cobicistat
	1.4	TAF 25 mg q.d. without boosting
	1.5	TAF 25 mg q.d. boosted with cobicistat or ritonavir
<b>Component 2</b> Pregnant WLHIV and HIV-uninfected women who received long-acting/extended release ARVs during pregnancy, and their infants	2.1	Long-acting injectable formulation of cabotegravir (CAB LA) any dose



Component	Arm	Drug or Drug Combination under Study
<b>Component 3</b> Pregnant WLHIV receiving ARVs and first-line TB treatment, and their infants	3.1	Dolutegravir (DTG) 50 mg b.i.d. when combined with RIF or 50 mg q.d. if RIF is not part of the TB regimen <b>and</b> at least two of the following TB treatment drugs: isoniazid (INH), rifampin (RIF), rifabutin (RFB), ethambutol (EMB), pyrazinamide (PZA), moxifloxacin (MFX)
	3.2	Atazanavir/ritonavir (ATV/r) $\geq$ 300/100 mg q.d. <b>or</b> darunavir/ritonavir (DRV/r) $\geq$ 600/100 mg b.i.d. <b>and</b> at least two of the following TB treatment drugs: INH, RIF, RFB, EMB, PZA, MFX
	3.3	Lopinavir/ritonavir (LPV/r) 800/200 mg b.i.d. <b>and</b> at least two of the following TB treatment drugs: INH, RIF, RFB, EMB, PZA, MFX
<b>Component 4</b> Pregnant WLHIV and HIV-uninfected women receiving second-line TB treatment, and their infants	4.1	At least one of the following TB treatment drugs: Levofloxacin (LFX) 750mg – 1000mg q.d.; Clofazimine (CFZ) 100mg q.d.; Linezolid (LZD) 300mg – 600mg q.d.; Bedaquiline (BDQ) 200mg t.i.w.; <b>or</b> Delamanid (DLM) 100mg b.i.d.; <b>or</b> Moxifloxacin (MFX) 400mg or 800mg q.d. <b>and</b> at least one other second-line TB treatment drug under study
	4.1	ARVs under study (WLHIV only) in combination with at least one of the above second-line TB treatment drugs: efavirenz, lopinavir, atazanavir, darunavir, dolutegravir, nevirapine, and/or raltegravir
<b>Component 5:</b> Postpartum WLHIV women breastfeeding while receiving oral ARVs, and their infants	5.1	ATV/r
	5.2	DRV/r
	5.3	LPV/r

## 5.1 Formulation of Drugs Under Study

Participants may receive innovator (i.e., brand name or non-generic) or generic formulations of ARVs and/or TB treatment drugs under study. Sites must follow procedures detailed in the IMPAACT 2026 MOP to obtain approval for enrollment of participants receiving a generic formulation of a drug under study; approval will be based on the extent to which generic formulations have a similar formulation, with similar expected bioavailability and drug release characteristics to the innovator formulation. All efforts should be made to ensure that participants receive the same product from the same manufacturer prior to all PK sampling periods. The name and manufacturer of each generic product will be entered into eCRFs.

## 5.2 Administration of Drugs Under Study

In general, drugs under study should be administered consistent with the package inserts and/or instructions provided by the non-study sources who prescribe or supply the drugs to participants. Study staff will provide participants with the dietary recommendations contained in [Appendix III](#). For participants receiving INSTIs (e.g. BIC, DTG) study staff will also provide information on co-administration of mineral-containing concomitant medications (including but not limited to prenatal vitamins) consistent with the INSTI package inserts.

For drugs administered orally, on each intensive or sparse PK sampling day, study staff will instruct the participants that the drug(s) under study will be administered on site after the pre-dose PK sample is drawn. Refer to [Section 6.10.1](#) for additional guidance around timing, procedures, and recording of doses of drugs under study for intensive and sparse PK visits. Refer to [Section 6.10.4](#) for additional guidance on administration of drugs under study for breast milk transfer PK.

## 5.3 Concomitant Medications

The term concomitant medications refers to medications other than the drugs under study listed in [Table 1](#) received by enrolled participants. This includes prescription and non-prescription (over-the-counter) medications; vaccines and other preventive medications; and alternative, complementary, and traditional medications and preparations. Concomitant medications must be source documented and entered into eCRFs, as part of the medical and medication histories obtained at each study visit, per guidance provided in [Sections 6.6](#) (maternal) and [6.9](#) (infant).

## 5.4 Disallowed Medications Prior to PK Sampling

The medications listed below in [Table 2](#) interfere with the PK profile of an ARV or TB drug and are disallowed for two weeks prior to PK sampling. The Core Protocol Team must be informed of any participant who requires a disallowed medication, and in consultation with the site investigator will determine if the participant should continue on study.

**Table 2. Disallowed Medications**

Drug Under Study	Disallowed Medications
BIC	<u>Anticonvulsants:</u> carbamazepine, oxcarbazepine, phenobarbital, phenytoin <u>Antimycobacterials:</u> rifabutin, rifampin, rifapentine <u>Herbal Products:</u> St. John's wort ( <i>Hypericum perforatum</i> ) <u>Medications or oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe),</u> unless BIC is administered while fasting a minimum of 2 hours prior to these medications: Calcium or iron supplements, Cation-containing antacids or laxatives, Sucralfate, Buffered medications
DOR	<u>Androgen Receptors:</u> enzalutamide <u>Anticonvulsants:</u> carbamazepine, oxcarbazepine, phenobarbital, phenytoin <u>Antimycobacterials:</u> rifampin, rifapentine, rifabutin <u>Cytotoxic Agents:</u> mitotane <u>HIV Antiviral Agents:</u> efavirenz, etravirine, nevirapine <u>Herbal Products:</u> St. John's wort ( <i>Hypericum perforatum</i> )

<b>Drug Under Study</b>	<b>Disallowed Medications</b>
<b>TAF</b>	<u>Anticonvulsants</u> : carbamazepine, oxcarbazepine, phenobarbital, phenytoin <u>Antimycobacterial</u> : rifabutin, rifampin, rifapentine <u>Herbal Products</u> : St. John's wort ( <i>Hypericum perforatum</i> )
<b>Cobicistat</b>	<u>Anticonvulsants</u> : carbamazepine, phenobarbital, phenytoin <u>Antifungals</u> : voriconazole <u>Endothelin Receptor Antagonists</u> : bosentan <u>HIV Antiviral Agents</u> : efavirenz, etravirine, nevirapine <u>Systemic oral corticosteroids</u> : dexamethasone
<b>DTG</b>	<u>Antiarrhythmic</u> : dofetilide <u>Anticonvulsants</u> : carbamazepine, oxcarbazepine, phenobarbital, phenytoin <u>Antimycobacterials</u> : rifampin (ALLOWED for TB arms [Arm 3.1]) <u>Herbal products</u> : St. John's wort ( <i>Hypericum perforatum</i> ) <u>Non-nucleosides</u> : delavirdine, efavirenz, etravirine, nevirapine <u>Protease Inhibitors</u> : atazanavir, darunavir, ritonavir, telaprevir, tipranavir <u>Medications or oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe)</u> , unless DTG administered 2 hours before or 6 hours after these medications: Calcium or iron supplements, Cation-containing antacids or laxatives, Sucralfate, Buffered medications
<b>ATV, DRV, ATV/r, DRV/r, LPV/r,</b>	<u>Antiarrhythmics</u> : Amiodarone, flecainide, propafenone, quinidine <u>Anticonvulsants</u> : carbamazepine, phenobarbital, phenytoin <u>Antihistamines</u> : astemizole, cisapride, terfenadine <u>Antimycobacterial</u> : rifampin, rifabutin (disallowed for ARV-only study arms, but allowed for women enrolled on the ARV/TB study arms) <u>Calcium channel blocker</u> : bepridil <u>Corticosteroids</u> : chronic oral dexamethasone <u>Ergot derivatives</u> : dihydroergotamine, ergotamine, ergonovine, methylegonovine <u>Herbal products</u> : St. John's wort ( <i>Hypericum perforatum</i> ) <u>HMG-CoA reductase inhibitors</u> : lovastatin, simvastatin <u>Neuroleptic</u> : pimozide <u>Non-nucleosides</u> : delavirdine, efavirenz, etravirine, nevirapine <u>Phosphodiesterase-5 inhibitor</u> : sildenafil for the treatment of pulmonary arterial hypertension <u>Sedative hypnotics</u> : triazolam, orally administered midazolam
<b>ATV/r and ATV (in addition to those listed above)</b>	<u>Antacids and buffered medications</u> , unless ATV is administered 2 hours before or 1 hour after these medications <u>Antifungals</u> : voriconazole <u>Antineoplastic</u> : irinotecan <u>HCV Antiviral Agents</u> : boceprevir <u>Protease inhibitor</u> : indinavir <u>Proton pump inhibitors</u> : esomeprazole, lansoprazole, omeprazole, rabeprazole
<b>DRV, DRV/r (in addition to those listed above)</b>	<u>Antiarrhythmic</u> : dronedarone <u>Anti-gout</u> : colchicine <u>Anti-anginal</u> : ranolazine <u>HCV Antiviral Agents</u> : simeprevir

Drug Under Study	Disallowed Medications
All ritonavir-containing regimens (in addition to those listed above)	<u>Antialcoholics</u> : disulfiram, metronidazole <u>Synthetic corticosteroid</u> : fluticasone
INH	<u>Antacids</u> : Aluminium hydroxide: take Al3+ antacids > 6 hours after isoniazid <u>Anti-anginals</u> : ranolazine <u>Antiarrhythmics</u> : dronedarone Disulfiram Multiple dosing of systemic corticosteroids
RIF	<u>Anticoagulants</u> : apixaban <u>Antifungals</u> : itraconazole, voriconazole Antiparasitals: artemether-lumefantrine, praziquantel <u>Calcium channel blocker</u> : nifedipine <u>Non-nucleosides</u> : delavirdine, etravirine, rilpivirine <u>Protease Inhibitors</u> : atazanavir, darunavir, <u>HCV Antiviral Agents</u> : sofosbuvir, simeprevir
RFB	<u>Antifungals</u> : itraconazole, voriconazole <u>Non-nucleosides</u> : delavirdine
EMB	Antacids: Aluminium hydroxide: take Al3+ antacids > 6 hours after ethambutol
PZA	No disallowed medications.
MFV	No disallowed medications.
LFV	No disallowed medications.
CFZ	No disallowed medications.
LZD	Rifamycins
BDQ	<u>Systemic use of moderate and strong CYP3A4 inhibitors</u> : azole antifungals such as ketoconazole, fluconazole, voriconazole, itraconazole; ketolides such as telithromycin; and macrolide antibiotics other than azithromycin and clarithromycin. <i>Note: Fluconazole is generally a less potent inhibitor of CYP3A4 than other azole antifungals; however, the effect of fluconazole on BDQ PK is unknown. For individual participants with a clinical need for fluconazole for greater than two weeks, this drug may be allowed. This decision should be made in consultation with the Core Protocol Team and attending clinicians.</i> <u>Systemic use of strong CYP3A4 inducers</u> : phenytoin, carbamazepine, phenobarbital, St. John's wort ( <i>Hypericum perforatum</i> ), rifamycins, and systemic multiple dosing of dexamethasone. <u>Non-nucleosides</u> : efavirenz
DLM	<u>Strong CYP 3A4 inducers</u> : carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifamycins

## 6 STUDY VISITS AND PROCEDURES

Maternal SoEs specific to each component are presented in [Appendix I-A](#) through [Appendix I-E](#). Infant SoEs are presented in [Appendix II-A](#) through [Appendix II-C](#). [Table 3](#) summarizes the SoEs

and consent forms to be used for each Component. Presented in this section is additional information on visit-specific study procedures for each Component. The term “informed consent” in this section is used to refer to both informed consent and assent for mothers who are not of legal age to provide independent consent.

**Table 3. Appendix Guideline for Schedules of Evaluations and Sample Informed Consent Forms**

Component	Participant Criteria	Schedules of Evaluations	Consent Forms
1	Pregnant WLHIV receiving oral ARVs and no TB drugs, and their infants	Appendix I-A (Maternal) Appendix II-A (Infant)	Appendix VI-A
2	WLHIV and HIV-uninfected women who received long-acting/extended release ARVs during pregnancy, and their infants	Appendix I-B (Maternal) Appendix II-B (Infant)	Appendix VI-B (Independent) Appendix VII (Parent/Guardian) Appendix VIII (Assent)
3	Pregnant WLHIV receiving ARVs and first-line TB treatment, and their infants	Appendix I-C (Maternal) Appendix II-A (Infant)	Appendix VI-C
4	Pregnant WLHIV and HIV-uninfected women receiving second-line TB treatment, and their infants	Appendix I-D (Maternal) Appendix II-A (Infant)	Appendix VI-D
5	Postpartum WLHIV breastfeeding while receiving oral ARVs, and their infants	Appendix I-E (Maternal) Appendix II-C (Infant)	Appendix VI-E

All visits and procedures must be performed at the approved clinical research site or approved associated facilities. All visits and procedures must be documented in accordance with the DAIDS policies for source documentation; refer to [Section 11](#) for more information on documentation requirements and entry of eCRFs. Refer to [Section 7](#) for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up.

In addition to the protocol-specified procedures described in this section and the SoE Appendices, study staff may complete other tasks consistent with site SOPs, including but not limited to collecting, reviewing, and updating demographic and locator information; reviewing elements of informed consent; scheduling telephone contacts and visits; providing instructions for contacting study staff between visits; providing visit reminders; and following up on missed visits. All such tasks should be documented consistent with site SOPs. Study staff should inform participants of clinically meaningful physical exam findings and laboratory test results when available.

## 6.1 Component 1 Study Visits and Procedures

### 6.1.1 Screening Procedures (Component 1)

Refer to [Section 4.7](#) for a description of the study recruitment, screening and enrollment process.

Screening procedures may be performed within 60 days prior to enrollment, up to and including the day of enrollment. Participants must provide consent before any activities are performed to determine eligibility. For potential participants who do not meet the eligibility criteria, screening should be discontinued once ineligibility is determined. Final eligibility determination and confirmation must precede enrollment.

<b>Screening Procedures (Component 1) (Within 60 days prior to enrollment)</b>	
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Obtain written informed consent/assent</li> <li>• Assign PIDs to mother and infant (fetus)</li> <li>• Obtain available documentation of mother’s HIV status</li> </ul>
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Assess documentation of HIV infection in relation to study requirements</li> <li>• Assess gestational age in relation to study requirements, based on best obstetrical method available (see the study-specific MOP for method of priority for gestational age determination)</li> <li>• Obtain available medical records and medical and medication history</li> <li>• Assess maternal ARV and TB drug history in relation to study requirements</li> </ul>
<b>Laboratory</b>	Collect blood for: <ul style="list-style-type: none"> <li>• Confirmatory HIV testing (<i>if needed per Section 4.5</i>)</li> </ul>

### 6.1.2 Second and/or Third Trimester Visit (Including Entry Visit) (Component 1)

Refer to [Section 4.7](#) for a description of the study recruitment, screening and enrollment process.

Entry may occur at the Second Trimester Visit between 20 and 0/7 weeks of pregnancy and 26 and 6/7 weeks of pregnancy, or at the Third Trimester Visit between 30 and 0/7 weeks of pregnancy and 37 and 6/7 weeks of pregnancy. Procedures that may provide information relevant to eligibility for the study should be performed first, prior to final eligibility determination. Final eligibility determination must precede enrollment. In the event that a woman is found to be ineligible on the day of enrollment, enrollment should not occur.

For women who are enrolled, initial PK sampling may be performed on the day of entry or on a different day consistent with the following requirements:

- If the participant is enrolled at the Second Trimester visit, initial PK sampling must occur between 20 and 0/7 weeks of pregnancy and 26 and 6/7 weeks of pregnancy.
- If the participant is enrolled at the Third Trimester visit, initial PK sampling must occur between 30 and 0/7 weeks of pregnancy and 37 and 6/7 weeks of pregnancy.
- The participant must have been on the drug(s) under study at the required dose for at least 2 weeks prior to initial PK sampling.
- Sites should make every effort to complete the initial PK sampling within five days after entry, but it must be performed no later than 14 days after enrollment.

Entry/2 <sup>nd</sup> Trimester/3 <sup>rd</sup> Trimester Visit Procedures (Component 1)		
Administrative and Regulatory		<ul style="list-style-type: none"> <li>Complete final eligibility determination and confirmation (Entry visit only, prior to enrollment)</li> <li>Complete paper-based eligibility checklist, enter checklist data into SES to enroll the mother-infant pair, print and file a copy of the confirmation file (Entry visit only)</li> </ul>
Clinical		<ul style="list-style-type: none"> <li>Obtain or update medical and medications history per <a href="#">Sections 6.6</a> and <a href="#">10.3</a> (at Entry Visit, perform prior to enrollment)</li> <li>Perform abbreviated physical exam</li> <li>Identify/review/update adverse events (at Third Trimester Visit only for participants enrolled during the second trimester)</li> </ul>
Laboratory	Blood	<p>Collect blood for:</p> <ul style="list-style-type: none"> <li><i>Arms 1.1 and 1.2</i>: Intensive PK sampling, per <a href="#">Section 6.10.1</a></li> <li><i>Arms 1.3, 1.4 and 1.5</i>: Sparse PK sampling with storage of plasma, DBS and PBMC per <a href="#">Section 6.10.1</a></li> <li>Chemistries: Albumin, BUN, creatinine, bilirubin, AST, ALT</li> <li>Hematology: hemoglobin, hematocrit</li> <li>CD4 cell count (Entry visit only)</li> <li>HIV RNA</li> <li>Alpha-1 acid glycoprotein: Measured at the pharmacology laboratory from PK pre-dose sample for highly protein bound drugs only</li> </ul> <p><i>For women who have consented to genetic testing:</i></p> <ul style="list-style-type: none"> <li>Store a DBS for pharmacogenetics, obtain from whole blood collected at any PK sampling time point (Entry visit only)</li> </ul>

### 6.1.3 Maternal Delivery Visit (Component 1)

The Maternal Delivery visit should be performed on the day of delivery. Except for the PK sampling (and samples obtained from PK specimens), other evaluations for this visit may be done four days prior to delivery through four days after delivery. The day of delivery is defined as Day 0 and all post-partum follow-up visits are scheduled from this date.

Maternal Delivery Visit Procedures (Component 1) (Day of Delivery ± 4 days)		
Clinical		<ul style="list-style-type: none"> <li>Update medical and medications history since last visit per <a href="#">Sections 6.6</a> and <a href="#">10.3</a></li> <li>Perform abbreviated physical exam</li> <li>Identify/review/update adverse events</li> </ul>
Laboratory	Blood	<p>Collect blood for:</p> <ul style="list-style-type: none"> <li>Single PK sample (delivery) per <a href="#">Section 6.10.2</a></li> <li>Cord blood PK sample, per <a href="#">Section 6.10.2</a></li> <li>Chemistries: BUN, creatinine, bilirubin, AST, ALT</li> <li>Hematology: hemoglobin, hematocrit</li> <li>HIV RNA</li> </ul> <p><i>Additionally, for women in Arms 1.3, 1.4, and 1.5 (TAF arms) only:</i></p> <ul style="list-style-type: none"> <li>Store DBS from maternal and cord blood PK sample</li> <li>Isolate PBMCs from maternal and cord blood PK sample (if possible, i.e. adequate volume is obtained and personnel are available for processing)</li> </ul>

### 6.1.4 Infant Birth Visit (Component 1)

The Infant Birth visit should be performed on the day of birth. PK sampling must be performed at specified time points; all other evaluations for this visit may be done within three days after birth. The day of birth is defined as Day 0 and all follow-up visits are scheduled from this date.

Infant Birth Visit Procedures (Component 1) (Day of Birth + 3 days)		
Clinical		<ul style="list-style-type: none"> <li>• Obtain baseline medical and medication and feeding history per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	<p><i>For infants undergoing washout PK sampling, collect blood for:</i></p> <ul style="list-style-type: none"> <li>• Infant washout PK sampling per <a href="#">Section 6.10.3</a></li> <li>• <i>Additionally, for infants in Arms 1.3, 1.4 and 1.5 (TAF arms):</i> store DBS from washout PK sample at each time point</li> <li>• <i>For infants for whom informed consent for genetic testing has also been obtained,</i> DBS storage for pharmacogenetics, obtain at either this visit OR at the 5-9 Days visit</li> </ul>

### 6.1.5 Maternal 6-12 Weeks Visit (Component 1)

The maternal 6-12 Weeks visit must take place within 42 and 90 days after delivery.

Maternal 6-12 Weeks Visit Procedures (Component 1)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medications history since last visit per <a href="#">Sections 6.6 and 10.3</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	<p>Collect blood for:</p> <ul style="list-style-type: none"> <li>• <i>Arms 1.1 and 1.2:</i> Intensive PK sampling, per <a href="#">Section 6.10.1</a></li> <li>• <i>Arms 1.3, 1.4 and 1.5:</i> Sparse PK sampling with storage of plasma, DBS and PBMC per <a href="#">Section 6.10.1</a></li> <li>• Chemistries: Albumin, BUN, creatinine, bilirubin, AST, ALT</li> <li>• Hematology: Hemoglobin, hematocrit</li> <li>• HIV RNA</li> <li>• Alpha-1 acid glycoprotein: Measured at the pharmacology laboratory from PK pre-dose sample for highly protein bound drugs only</li> </ul>

### 6.1.6 Infant 16-24 Weeks Visit (Component 1)

The infant 16-24 Weeks visit is targeted to take place within 112 and 174 days after birth, with an allowable window of up to 204 days to complete data collection from the medical record. Data may be abstracted from the participant chart at any point that it is available within the allowable window for the visit.

Infant 16-24 Weeks Visit Procedures (Component 1)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medication and feeding history since last visit per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>



## 6.2 Component 2 Study Visits and Procedures

### 6.2.1 Screening and Entry Visit (Component 2)

Refer to [Section 4.7](#) for a description of the study recruitment, screening and enrollment process.

Screening and Entry procedures may be performed from 24 0/7 weeks of pregnancy through the day of delivery; however, enrollment must occur prior to delivery. Participants must provide consent before any activities are performed to determine eligibility. Final eligibility determination must precede enrollment. For potential participants who do not meet the eligibility criteria, screening should be discontinued once ineligibility is determined. In the event that a woman is found to be ineligible on the day of enrollment, enrollment should not occur.

<b>Screening and Entry Procedures (Component 2) (Week 24 0/7 of pregnancy through day of delivery)</b>	
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"><li>• Obtain written informed consent/assent*</li><li>• Assign PIDs to mother and infant (fetus)*</li><li>• Complete final eligibility determination and confirmation (Entry visit only)*</li><li>• Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the mother-infant pair, print and file a copy of the confirmation file (Entry visit only)</li></ul>
<b>Clinical</b>	<ul style="list-style-type: none"><li>• Assess gestational age in relation to study requirements, based on best obstetrical method available (see study-specific MOP for method of priority for gestational age determination)*</li><li>• Obtain available medical records and medical and medication history*</li><li>• Assess maternal ARV history in relation to study requirements*</li><li>• Perform abbreviated physical exam (Entry visit only)</li></ul>

\*Perform prior to enrollment

### 6.2.2 Maternal Delivery Visit (Component 2)

The Maternal Delivery Visit should be performed on the day of delivery. Except for the PK sampling (and samples obtained from PK specimens), other evaluations for this visit may be done four days prior to delivery through four days after delivery.

The day of delivery is defined as Day 0 and all post-partum follow-up visits are scheduled from this date.

<b>Maternal Delivery Visit Procedures (Component 2) (Day of Delivery ± 4 days)</b>		
<b>Clinical</b>		<ul style="list-style-type: none"> <li>• Update medical and medications history since last visit per <a href="#">Sections 6.6</a> and <a href="#">10.3</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
<b>Laboratory</b>	<b>Blood</b>	Collect blood for: <ul style="list-style-type: none"> <li>• Single PK sample (delivery) per <a href="#">Section 6.10.2</a></li> <li>• Cord blood PK sample, per <a href="#">Section 6.10.2</a></li> <li>• Chemistries: Albumin, BUN, creatinine, bilirubin, AST, ALT</li> <li>• Hematology: hemoglobin, hematocrit</li> <li>• Alpha-1 acid glycoprotein: Measured at the pharmacology laboratory from delivery PK sample for highly protein bound drugs only</li> </ul> <i>For women who have consented to genetic testing:</i> <ul style="list-style-type: none"> <li>• Store a DBS for pharmacogenetics, obtain from whole blood from PK sample</li> </ul>

### 6.2.3 Infant Birth Visit (Component 2)

The Infant Birth Visit should be performed on the day of birth. PK sampling must be performed at specified time points; all other evaluations for this visit may be done within three days after birth. The day of birth is defined as Day 0 and all follow-up visits are scheduled from this date.

<b>Infant Birth Visit Procedures (Component 2) (Day of Birth + 3 days)</b>		
<b>Clinical</b>		<ul style="list-style-type: none"> <li>• Obtain baseline medical and medication and feeding history per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
<b>Laboratory</b>	<b>Blood</b>	<i>For infants undergoing washout PK sampling, collect blood for:</i> <ul style="list-style-type: none"> <li>• Infant washout PK sampling per <a href="#">Section 6.10.3</a></li> <li>• <i>For infants for whom informed consent for genetic testing has also been obtained:</i> store DBS for pharmacogenetics, obtain at either this visit OR at the 5-9 Days visit</li> </ul>

### 6.2.4 Maternal 5-9 Days and Infant 5-9 Days Visits (Component 2)

The maternal 5-9 Days visit must take place within 5-9 days after delivery. Only women who meet the requirements for breast milk transfer PK sampling per [Section 6.10.4](#) will complete this visit.

The infant 5-9 Days visit must take place within 5-9 days after birth. Only infants who meet the requirements for infant washout PK sampling per [Section 6.10.3](#) will complete this visit. For infants who also meet requirements for breast milk transfer PK per [Section 6.10.4](#), drug concentrations for breast milk transfer PK assessments will be measured from the washout PK sample at these visits.

For mother-infant pairs undergoing breast milk transfer PK sampling, the maternal and infant visits must be coordinated such that breast milk, maternal blood and infant blood are all collected within a ninety-minute period.

Maternal 5-9 Days Visit Procedures (Component 2)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medications history since last visit per <a href="#">Sections 6.6 and 10.3</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	Collect blood for <ul style="list-style-type: none"> <li>• Single PK sample (breast milk transfer PK) per <a href="#">Section 6.10.4*</a></li> </ul>
	Breast milk	Collect breast milk for: <ul style="list-style-type: none"> <li>• Breast milk transfer PK per <a href="#">Section 6.10.4*</a></li> </ul>

Infant 5-9 Days Visit Procedures (Component 2)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medication and feeding history since last visit, per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	<i>For infants undergoing washout PK sampling, collect blood for:</i> <ul style="list-style-type: none"> <li>• Infant washout PK sampling per <a href="#">Section 6.10.3</a> (<i>If mother-infant pair is also eligible for breast milk transfer PK, the drug concentrations measured from this sample will be used for infants undergoing breast milk transfer, but collection must be within ninety minutes of the first of the infant blood, maternal blood, or breast milk sample collection</i>)*</li> <li>• <i>For infants for whom informed consent for genetic testing has also been obtained: DBS storage for pharmacogenetics, if not previously collected at the Birth Visit</i></li> </ul>

\* Maternal blood, breast milk, and infant blood must be all be collected within ninety minutes of the first of these three samples that is collected.

## 6.2.5 Maternal 12-16 Days and Infant 12-16 Days Visits (Component 2)

The maternal 12-16 Days visit must take place within 12-16 days after delivery. Only women who meet the requirements for breast milk transfer PK sampling per [Section 6.10.4](#) will complete this visit.

The infant 12-16 Days visit will take place 12-16 days after birth. Only infants who meet the requirements for infant washout PK sampling per [Section 6.10.3](#) will complete this visit. For infants who also meet requirements for breast milk transfer PK per [Section 6.10.4](#), drug concentrations for breast milk transfer PK assessments will be measured from the washout PK sample at these visits.

For mother-infant pairs undergoing breast milk transfer PK sampling, the maternal and infant visits must be coordinated such that breast milk, maternal blood and infant blood are all collected within a ninety-minute period.

Maternal 12-16 Days Visit Procedures (Component 2)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medications history since last visit (per <a href="#">Sections 6.6 and 10.3</a>)</li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> <li>• Single PK sample (breast milk transfer PK) per <a href="#">Section 6.10.4*</a></li> </ul>
	Breast milk	Collect breast milk for: <ul style="list-style-type: none"> <li>• Breast milk transfer PK per <a href="#">Section 6.10.4*</a></li> </ul>

Infant 12-16 Days Visit Procedures (Component 2)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medication and feeding history since last visit per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	<p><i>For infants undergoing washout PK sampling, collect blood for:</i></p> <ul style="list-style-type: none"> <li>• Infant washout PK sampling per <a href="#">Section 6.10.3</a> (If mother-infant pair is also eligible for breast milk transfer PK, the drug concentrations measured from this sample will be used for infants undergoing breast milk transfer, but collection must be within ninety minutes of the first of the infant blood, maternal blood, or breast milk sample collection)*</li> </ul>

\* Maternal blood, breast milk, and infant blood must be all be collected within ninety minutes of the first of these three samples collected.

### 6.2.6 Maternal 3-5 Weeks and Infant 3-5 Weeks Visits (Component 2)

The maternal 3-5 Weeks visit must take place within 21 and 41 days after delivery. Only women who meet the requirements for breast milk transfer PK sampling per [Section 6.10.4](#) will complete this visit.

The infant 3-5 Weeks visit must take place within 21 and 41 days after birth. Only infants who meet the requirements for breast milk transfer PK sampling per [Section 6.10.4](#) will complete this visit.

The maternal and infant visits must be coordinated such that breast milk, maternal blood and infant blood are all collected within a ninety-minute period.

Maternal 3-5 Weeks Visit Procedures (Component 2)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medications history since last visit (per <a href="#">Sections 6.6</a> and <a href="#">10.3</a>)</li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	<p>Collect blood for:</p> <ul style="list-style-type: none"> <li>• Single PK sample (breast milk transfer PK) per <a href="#">Section 6.10.4</a>*</li> </ul>
	Breast milk	<p>Collect breast milk for:</p> <ul style="list-style-type: none"> <li>• Breast milk transfer PK per <a href="#">Section 6.10.4</a>*</li> </ul>

Infant 3-5 Weeks Visit Procedures (Component 2)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medication and feeding history since last visit per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	<p>Collect blood for:</p> <ul style="list-style-type: none"> <li>• Breast milk transfer PK sample per <a href="#">Section 6.10.4</a>*</li> </ul>

\* Maternal blood, breast milk, and infant blood must be all be collected within ninety minutes of the first of these three samples that is drawn.

## 6.3 Component 3 Study Visits and Procedures

### 6.3.1 Screening Procedures (Component 3)

Refer to [Section 4.7](#) for a description of the study recruitment, screening and enrollment process.

Screening procedures may be performed within 60 days prior to enrollment, up to and including the day of enrollment. Participants must provide consent before any activities are performed to determine eligibility. For potential participants who do not meet the eligibility criteria, screening should be discontinued once ineligibility is determined. Final eligibility determination and confirmation must precede enrollment.

<b>Screening Procedures (Component 3) (Within 60 days prior to enrollment)</b>	
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Obtain written informed consent/assent</li> <li>• Assign PIDs to mother and infant (fetus)</li> <li>• Obtain available documentation of mother’s HIV status</li> </ul>
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Assess documentation of HIV infection in relation to study requirements</li> <li>• Assess gestational age in relation to study requirements, based on best obstetrical method available (see the study-specific MOP for method of priority for gestational age determination)</li> <li>• Obtain available medical records and medical and medication history</li> <li>• Assess maternal ARV and TB treatment drug history in relation to study requirements</li> </ul>
<b>Laboratory</b>	Collect blood for: <ul style="list-style-type: none"> <li>• Confirmatory HIV testing (<i>if needed per Section 4.5</i>)</li> </ul>

### 6.3.2 Second and/or Third Trimester Visit (Including Entry Visit) (Component 3)

Refer to [Section 4.7](#) for a description of the study recruitment, screening and enrollment process.

Entry may occur at the Second Trimester visit between 20 and 0/7 weeks of pregnancy and 26 and 6/7 weeks of pregnancy, or at the Third Trimester visit between 30 and 0/7 weeks of pregnancy and 37 and 6/7 weeks of pregnancy. Procedures that may provide information relevant to eligibility for the study should be performed first, prior to final eligibility determination. Final eligibility determination must precede enrollment. In the event that a woman is found to ineligible on the day of enrollment, enrollment should not occur.

For women who are enrolled, initial PK sampling may be performed on the day of entry or on a different day consistent with the following requirements:

- If the participant is enrolled at the Second Trimester visit, initial PK sampling must occur between 20 and 0/7 weeks of pregnancy and 26 and 6/7 weeks of pregnancy.
- If the participant is enrolled at the Third Trimester visit, initial PK sampling must occur between 30 and 0/7 weeks of pregnancy and 37 and 6/7 weeks of pregnancy.
- The participant must have been on the drug(s) under study at the required dose for at least 2 weeks prior to PK sampling.
- Sites should make every effort to complete the initial PK sampling within five days after enrollment, but it must be performed no later than 14 days after enrollment.

Entry/2 <sup>nd</sup> Trimester/3 <sup>rd</sup> Trimester Visit Procedures (Component 3)		
<b>Administrative and Regulatory</b>		<ul style="list-style-type: none"> <li>• Complete final eligibility determination and confirmation (Entry visit only, prior to enrollment)</li> <li>• Complete paper-based eligibility checklist, enter checklist data into SES to enroll the mother-infant pair, print and file a copy of the confirmation file (Entry visit only)</li> </ul>
<b>Clinical</b>		<ul style="list-style-type: none"> <li>• Obtain medical and medications history per <a href="#">Sections 6.6</a> and <a href="#">10.3</a> (at Entry Visit, perform prior to enrollment)</li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events (at Third Trimester Visit only for participants enrolled during the second trimester)</li> </ul>
<b>Laboratory</b>	<b>Blood</b>	Collect blood for: <ul style="list-style-type: none"> <li>• Intensive ARV and TB drug PK sampling per <a href="#">Section 6.10.1</a></li> <li>• Chemistries: Albumin, BUN, creatinine, bilirubin, AST, ALT</li> <li>• Hematology: Complete blood count (CBC) and absolute neutrophil count (ANC)</li> <li>• CD4 cell count (Entry visit only)</li> <li>• HIV RNA</li> <li>• Alpha-1 acid glycoprotein: Measured at the pharmacology laboratory from PK pre-dose sample</li> </ul> <p><i>For women who have consented to genetic testing:</i></p> <ul style="list-style-type: none"> <li>• Store a DBS for pharmacogenetics, obtain from whole blood collected at any PK sampling time point (Entry visit only)</li> </ul>

### 6.3.3 Maternal Delivery Visit (Component 3)

The Maternal Delivery Visit should be performed on the day of delivery. Except for the PK sampling (and samples obtained from PK specimens), other evaluations for this visit may be done four days prior to delivery through four days after delivery. The day of delivery is defined as Day 0 and all post-partum follow-up visits are scheduled from this date.

Maternal Delivery Visit Procedures (Component 3) (Day of Delivery ± 4 days)		
<b>Clinical</b>		<ul style="list-style-type: none"> <li>• Update medical and medications history since last visit per <a href="#">Sections 6.6</a> and <a href="#">10.3</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
<b>Laboratory</b>	<b>Blood</b>	Collect blood for: <ul style="list-style-type: none"> <li>• Single PK sample (delivery) per <a href="#">Section 6.10.2</a></li> <li>• Cord blood sample, per <a href="#">Section 6.10.2</a></li> <li>• Chemistries: BUN, creatinine, bilirubin, AST, ALT</li> <li>• Hematology: CBC and ANC</li> <li>• HIV RNA</li> </ul>

### 6.3.4 Infant Birth Visit (Component 3)

The Infant Birth Visit should be performed on the day of birth. PK sampling must be performed at specified time points; all other evaluations for this visit may be done within three days after birth. The day of birth is defined as Day 0 and all follow-up visits are scheduled from this date.

Infant Birth Visit Procedures (Component 3) (Day of Birth + 3 days)		
Clinical		<ul style="list-style-type: none"> <li>• Obtain baseline medical and medication and feeding history per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	<p><i>For infants undergoing washout PK sampling, collect blood for:</i></p> <ul style="list-style-type: none"> <li>• Infant washout PK sampling per <a href="#">Section 6.10.3</a></li> <li>• <i>For infants for whom informed consent for genetic testing has also been obtained, DBS storage for pharmacogenetics, obtain at either this visit OR at the 5-9 Days visit</i></li> </ul>

### 6.3.5 Maternal 5-9 Days and Infant 5-9 Days Visits (Component 3)

The maternal 5-9 Days visit must take place within 5-9 days after delivery. Only women in arms 3.2 or 3.3 who meet the requirements for breast milk transfer PK sampling per [Section 6.10.4](#) will complete this visit. Breast milk transfer PK sampling will not be performed in Arm 3.1.

The infant 5-9 Days visit must take place within 5-9 days after birth. Only infants who meet the requirements for infant washout PK sampling per [Section 6.10.3](#) will complete this visit. Breast milk transfer PK sampling will also be conducted at this visit for infants who meet the requirements per [Section 6.10.4](#).

For mother-infant pairs undergoing breast milk transfer PK sampling, the maternal and infant visits must be coordinated such that breast milk, maternal blood and infant blood are all collected within a ninety-minute period.

Maternal 5-9 Days Visit Procedures (Component 3)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medications history since last visit, per <a href="#">Sections 6.6</a> and <a href="#">10.3</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	<p>Collect blood for:</p> <ul style="list-style-type: none"> <li>• Single PK sample (breast milk transfer PK) per <a href="#">Section 6.10.4*</a></li> </ul>
	Breast milk	<p>Collect breast milk for:</p> <ul style="list-style-type: none"> <li>• Breast milk transfer PK sample per <a href="#">Section 6.10.4*</a></li> </ul>

Infant 5-9 Days Visit Procedures (Component 3)		
Clinical		<ul style="list-style-type: none"> <li>• Perform abbreviated physical exam</li> <li>• Update medical and medication and feeding history since last visit per <a href="#">Section 6.9</a></li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	<p><i>For infants undergoing washout PK sampling, collect blood for:</i></p> <ul style="list-style-type: none"> <li>• Infant washout PK sampling per <a href="#">Section 6.10.3</a> (<i>If mother-infant pair is also eligible for breast milk transfer PK, the drug concentrations measured from this sample will be used for infants undergoing breast milk transfer, but collection must be within ninety minutes of the first of the infant blood, maternal blood, or breast milk sample collection</i>)*</li> <li>• <i>For infants for whom informed consent for genetic testing has also been obtained: DBS storage for pharmacogenetics, if not previously collected at the Birth Visit</i></li> </ul>

\* Maternal blood, breast milk, and infant blood must be all be collected within ninety minutes of the first of these three samples collected.

### 6.3.6 Maternal 2-8 Weeks and Infant 2-8 Weeks Visits (Component 3)

The maternal 2-8 Weeks visit must take place within 14 and 62 days after delivery. All maternal participants are expected to complete this visit.

The infant 2-8 Weeks visit must take place within 14 and 62 days after birth. Only infants enrolled in arms 3.2 or 3.3 who meet the requirements for breast milk transfer PK sampling per [Section 6.10.4](#) will complete this visit.

For mother-infant pairs undergoing breast milk transfer PK sampling, the maternal and infant visits must occur on the same date within both the maternal and infant visit windows and be coordinated such that breast milk and infant blood are collected within ninety minutes of the 2-hour post dose maternal intensive PK sample.

Maternal 2-8 Weeks Visit Procedures (Component 3)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medications history since last visit per <a href="#">Sections 6.6</a> and <a href="#">10.3</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> <li>• Intensive ARV and TB drug PK sampling per <a href="#">Section 6.10.1</a></li> <li>• Chemistries: Albumin, BUN, creatinine, bilirubin, AST, ALT</li> <li>• Hematology: CBC with ANC</li> <li>• Alpha-1 acid glycoprotein: Measured at the pharmacology laboratory from PK pre-dose sample</li> <li>• HIV RNA</li> </ul>
	Breast milk	<i>For women in arms 3.2 or 3.3 undergoing breast milk transfer PK sampling,</i> collect breast milk for: <ul style="list-style-type: none"> <li>• Breast milk transfer PK per <a href="#">Section 6.10.4</a>. (Collect within ninety minutes of the 2-hour post-dose maternal intensive PK sample).</li> </ul>

Infant 2-8 Weeks Visit Procedures (Component 3)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medication and feeding history since last visit per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> <li>• Breast milk transfer PK sample per <a href="#">Section 6.10.4</a>. (Collect within ninety minutes of the maternal 2-hour post-dose sample).</li> </ul>

### 6.3.7 Maternal and Infant 16-24 Weeks Visits (Component 3)

The maternal 16-24 Weeks visit must take place within 112 and 174 days after delivery. Only women in arms 3.2 or 3.3 who meet the requirements for breast milk transfer PK sampling per [Section 6.10.4](#) will complete this visit.

The infant 16-24 Weeks visit is targeted to take place within 112 and 174 days after birth, with an allowable window of up to 204 days to complete data collection from the medical record.

For mother-infant pairs undergoing breast milk transfer PK sampling, the maternal and infant visits should be coordinated such that breast milk, maternal blood and infant blood are collected



within a ninety-minute period. For all other infants, data may be abstracted from the participant chart at any point that it is available within the allowable window for the visit.

<b>Maternal 16-24 Weeks Visit Procedures (Component 3)</b>		
<b>Clinical</b>		<ul style="list-style-type: none"> <li>• Update medical and medications history since last visit per <a href="#">Sections 6.6</a> and <a href="#">10.3</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
<b>Laboratory</b>	<b>Blood</b>	Collect blood for: <ul style="list-style-type: none"> <li>• Single PK sample (breast milk transfer PK) per <a href="#">Section 6.10.4*</a></li> </ul>
	<b>Breast milk</b>	Collect breast milk for: <ul style="list-style-type: none"> <li>• Breast milk transfer PK per <a href="#">Section 6.10.4*</a></li> </ul>

<b>Infant 16-24 Weeks Visit Procedures (Component 3)</b>		
<b>Clinical</b>		<ul style="list-style-type: none"> <li>• Update medical and medication and feeding history since last visit per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
<b>Laboratory</b>	<b>Blood</b>	<i>For infants undergoing breast milk transfer PK sampling, collect blood for:</i> <ul style="list-style-type: none"> <li>• Breast milk transfer PK sample per <a href="#">Section 6.10.4*</a></li> </ul>

\* Maternal blood, breast milk, and infant blood must be all be collected within ninety minutes of the first of these three samples collected.

## 6.4 Component 4 Study Visits and Procedures

### 6.4.1 Screening Procedures (Component 4)

Refer to [Section 4.7](#) for a description of the study recruitment, screening and enrollment process.

Screening procedures may be performed within 60 days prior to enrollment, up to and including the day of enrollment. Participants must provide consent before any activities are performed to determine eligibility. For potential participants who do not meet the eligibility criteria, screening should be discontinued once ineligibility is determined. Final eligibility determination and confirmation must precede enrollment.

<b>Screening Procedures (Component 4) (Within 60 days prior to enrollment)</b>		
<b>Administrative and Regulatory</b>		<ul style="list-style-type: none"> <li>• Obtain written informed consent/assent</li> <li>• Assign PIDs to mother and infant (fetus)</li> <li>• Obtain available documentation of mother's HIV status</li> </ul>
<b>Clinical</b>		<ul style="list-style-type: none"> <li>• Assess documentation of HIV infection in relation to study requirements</li> <li>• Assess gestational age in relation to study requirements, based on best obstetrical method available (see the study-specific MOP for method of priority for gestational age determination)</li> <li>• Obtain available medical records and medical and medication history</li> <li>• Assess maternal ARV and TB drug history in relation to study requirements</li> </ul>
<b>Laboratory</b>		Collect blood for: <ul style="list-style-type: none"> <li>• Confirmatory HIV testing (<i>if needed per <a href="#">Section 4.5</a></i>)</li> </ul>

## 6.4.2 Second and/or Third Trimester Visit (Including Entry Visit) (Component 4)

Refer to [Section 4.7](#) for a description of the study recruitment, screening and enrollment process.

Entry may occur at the Second Trimester Visit between 20 and 0/7 weeks of pregnancy and 26 and 6/7 weeks of pregnancy; or at the Third Trimester Visit between 30 and 0/7 weeks of pregnancy and 37 and 6/7 weeks of pregnancy. Procedures that may provide information relevant to eligibility for the study should be performed first, prior to final eligibility determination. Final eligibility determination must precede enrollment. In the event that a woman is found to be ineligible on the day of enrollment, enrollment should not occur.

For women who are enrolled, initial PK sampling may be performed on the day of entry or on a different day consistent with the following requirements:

- If the participant is enrolled at the Second Trimester visit, initial PK sampling must occur between 20 and 0/7 weeks of pregnancy and 26 and 6/7 weeks of pregnancy.
- If the participant is enrolled at the Third Trimester visit, initial PK sampling must occur between 30 and 0/7 weeks of pregnancy and 37 and 6/7 weeks of pregnancy.
- The participant must have been on the drug(s) under study at the required dose for at least 2 weeks prior to initial PK sampling.
- Sites should make every effort to complete the initial PK sampling within five days after entry, but it must be performed no later than 14 days after enrollment.

Entry/2 <sup>nd</sup> Trimester/3 <sup>rd</sup> Trimester Visit Procedures (Component 4)					
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Complete final eligibility determination and confirmation (Entry visit only, prior to enrollment)</li> <li>• Complete paper-based eligibility checklist, enter checklist data into SES to enroll the mother-infant pair, print and file a copy of the confirmation file (Entry visit only)</li> </ul>				
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Obtain or update medical and medications history per <a href="#">Sections 6.6</a> and <a href="#">10.3</a> (at Entry Visit, perform prior to enrollment)</li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events (at Third Trimester Visit only for participants enrolled during the second trimester)</li> </ul>				
<b>Laboratory</b>	<table border="1"> <thead> <tr> <th>Blood</th> <th></th> </tr> </thead> <tbody> <tr> <td></td> <td>           Collect blood for:           <ul style="list-style-type: none"> <li>• Intensive TB drug PK sampling per <a href="#">Section 6.10.1</a></li> <li>• <i>Additionally, for WLHIV who are taking ARVs under study:</i> Intensive ARV PK sampling per <a href="#">Section 6.10.1</a></li> <li>• Chemistries: Albumin, BUN, creatinine, bilirubin, AST, ALT, electrolytes [potassium (K), magnesium (Mg), calcium (Ca)]</li> <li>• Hematology: CBC and ANC</li> <li>• Alpha-1 acid glycoprotein: Measured at the pharmacology laboratory from PK pre-dose sample</li> <li>• <i>WLHIV only:</i> CD4 cell count (Entry visit only)</li> <li>• <i>WLHIV only:</i> HIV RNA</li> </ul>   <i>For women who have consented for genetic testing:</i> <ul style="list-style-type: none"> <li>• Store DBS for pharmacogenetics, obtain from whole blood collected at any PK sampling time point (Entry visit only)</li> </ul> </td> </tr> </tbody> </table>	Blood			Collect blood for: <ul style="list-style-type: none"> <li>• Intensive TB drug PK sampling per <a href="#">Section 6.10.1</a></li> <li>• <i>Additionally, for WLHIV who are taking ARVs under study:</i> Intensive ARV PK sampling per <a href="#">Section 6.10.1</a></li> <li>• Chemistries: Albumin, BUN, creatinine, bilirubin, AST, ALT, electrolytes [potassium (K), magnesium (Mg), calcium (Ca)]</li> <li>• Hematology: CBC and ANC</li> <li>• Alpha-1 acid glycoprotein: Measured at the pharmacology laboratory from PK pre-dose sample</li> <li>• <i>WLHIV only:</i> CD4 cell count (Entry visit only)</li> <li>• <i>WLHIV only:</i> HIV RNA</li> </ul> <i>For women who have consented for genetic testing:</i> <ul style="list-style-type: none"> <li>• Store DBS for pharmacogenetics, obtain from whole blood collected at any PK sampling time point (Entry visit only)</li> </ul>
Blood					
	Collect blood for: <ul style="list-style-type: none"> <li>• Intensive TB drug PK sampling per <a href="#">Section 6.10.1</a></li> <li>• <i>Additionally, for WLHIV who are taking ARVs under study:</i> Intensive ARV PK sampling per <a href="#">Section 6.10.1</a></li> <li>• Chemistries: Albumin, BUN, creatinine, bilirubin, AST, ALT, electrolytes [potassium (K), magnesium (Mg), calcium (Ca)]</li> <li>• Hematology: CBC and ANC</li> <li>• Alpha-1 acid glycoprotein: Measured at the pharmacology laboratory from PK pre-dose sample</li> <li>• <i>WLHIV only:</i> CD4 cell count (Entry visit only)</li> <li>• <i>WLHIV only:</i> HIV RNA</li> </ul> <i>For women who have consented for genetic testing:</i> <ul style="list-style-type: none"> <li>• Store DBS for pharmacogenetics, obtain from whole blood collected at any PK sampling time point (Entry visit only)</li> </ul>				

### 6.4.3 Maternal Delivery Visit (Component 4)

The Maternal Delivery Visit should be performed on the day of delivery. Except for the PK sampling (and samples obtained from PK specimens), other evaluations for this visit may be done four days prior to delivery through four days after delivery. The day of delivery is defined as Day 0 and all post-partum follow-up visits are scheduled from this date.

Maternal Delivery Visit Procedures (Component 4) (Day of Delivery ± 4 days)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medications history since last visit per <a href="#">Sections 6.6 and 10.3</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> <li>• Single PK sample (delivery), per <a href="#">Section 6.10.2</a></li> <li>• Cord blood sample per <a href="#">Section 6.10.2</a></li> <li>• Chemistries: BUN, creatinine, bilirubin, AST, ALT, electrolytes (K, Mg, Ca)</li> <li>• Hematology: CBC and ANC</li> <li>• <i>WLHIV only</i>: HIV RNA</li> </ul>

### 6.4.4 Infant Birth Visit (Component 4)

The Infant Birth Visit should be performed on the day of birth. PK sampling must be performed at specified time points; all other evaluations for this visit may be done within three days after birth. The day of birth is defined as Day 0 and all follow-up visits are scheduled from this date.

Infant Birth Visit Procedures (Component 4) (Day of Birth + 3 days)		
Clinical		<ul style="list-style-type: none"> <li>• Obtain baseline medical and medication and feeding history per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	<i>For infants undergoing washout PK sampling, collect blood for:</i> <ul style="list-style-type: none"> <li>• Infant washout PK sampling per <a href="#">Section 6.10.3</a></li> <li>• <i>For infants for whom informed consent for genetic testing has also been obtained, DBS storage for pharmacogenetics, obtain at either this visit OR at the 5-9 Days visit</i></li> </ul>

### 6.4.5 Maternal 5-9 Days and Infant 5-9 Days Visits (Component 4)

The maternal 5-9 Days visit must take place within 5-9 days after delivery. Only women who meet the requirements for breast milk transfer PK sampling per [Section 6.10.4](#) will complete this visit.

The infant 5-9 Days visit must take place within 5-9 days after birth. Only infants who meet the requirements for infant washout PK sampling per [Section 6.10.3](#) will complete this visit. Breast milk transfer PK sampling will also be conducted at this visit for infants who meet the requirements per [Section 6.10.4](#).

For mother-infant pairs undergoing breast milk transfer PK sampling, the maternal and infant visits must be coordinated such that breast milk, maternal blood and infant blood are all collected within a ninety-minute period.

Maternal 5-9 Days Visit Procedures (Component 4)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medications history since last visit per <a href="#">Sections 6.6 and 10.3</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> <li>• Single PK sample (breast milk transfer PK) per <a href="#">Section 6.10.4*</a></li> </ul>
	Breast milk	Collect breast milk for: <ul style="list-style-type: none"> <li>• Breast milk transfer PK per <a href="#">Section 6.10.4*</a></li> </ul>

Infant 5-9 Days Visit Procedures (Component 4)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medication and feeding history since last visit per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	<i>For infants undergoing washout PK sampling, collect blood for:</i> <ul style="list-style-type: none"> <li>• Infant washout PK sampling per <a href="#">Section 6.10.3</a> (<i>If mother-infant pair is also eligible for breast milk transfer PK, the drug concentrations measured from this sample will be used for infants undergoing breast milk transfer, but collection must be within ninety minutes of the first of the infant blood, maternal blood, or breast milk sample collection</i>)*</li> <li>• <i>For infants for whom informed consent for genetic testing has also been obtained: DBS storage for pharmacogenetics, if not previously collected at the Birth Visit.</i></li> </ul>

\* Maternal blood, breast milk, and infant blood must be all be collected within ninety minutes of the first of these three samples that is drawn.

#### 6.4.6 Maternal 2-8 Weeks and Infant 2-8 Weeks Visits (Component 4)

The maternal 2-8 Weeks visit must take place within 14 and 62 days after delivery. All maternal participants are expected to complete this visit.

The infant 2-8 Weeks visit must take place within 14 and 62 days after birth. Only infants who meet the requirements for breast milk transfer PK sampling per [Section 6.10.4](#) will complete this visit.

For mother-infant pairs undergoing breast milk transfer PK sampling, the maternal and infant visits must occur on a date that is within both the maternal and infant visit windows, and be coordinated such that breast milk and infant blood are collected within ninety minutes of the 2-hour post dose maternal intensive PK sampling.

Maternal 2-8 Weeks Visit Procedures (Component 4)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medications history since last visit per <a href="#">Sections 6.6</a> and <a href="#">10.3</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> <li>• Intensive TB drug PK sampling per <a href="#">Section 6.10.1</a></li> <li>• <i>Additionally, for WLHIV who are taking ARVs under study:</i> Intensive ARV PK sampling per <a href="#">Section 6.10.1</a></li> <li>• Chemistries: Albumin, BUN, creatinine, bilirubin, AST, ALT, electrolytes (K, Mg, Ca)</li> <li>• Hematology: CBC and ANC.</li> <li>• Alpha-1 acid glycoprotein: Measured at the pharmacology laboratory from PK pre-dose sample</li> <li>• <i>WLHIV only:</i> HIV RNA</li> </ul>
	Breast milk	<i>For women undergoing breast milk transfer PK sampling, collect breast milk for:</i> <ul style="list-style-type: none"> <li>• Breast milk transfer PK per <a href="#">Section 6.10.4</a>. (Collect within ninety minutes of the 2-hour post-dose maternal intensive PK sample)</li> </ul>

Infant 2-8 Weeks Visit Procedures (Component 4)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medication and feeding history since last visit per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> <li>• Breast milk transfer PK sample per <a href="#">Section 6.10.4</a>. Collect within ninety minutes of the maternal 2-hour post-dose sample collection</li> </ul>

#### 6.4.7 Maternal 16-24 Weeks and Infant 16-24 Weeks Visits (Component 4)

The maternal 16-24 Weeks visit must take place within 112 and 174 days after delivery. Only women who meet the requirements for breast milk transfer PK sampling per [Section 6.10.4](#) will complete this delivery visit.

The infant 16-24 Weeks visit is targeted to take place within 112 and 174 days after birth, with an allowable window of up to 204 days to complete data collection from the medical record.

For mother-infant pairs undergoing breast milk transfer PK sampling, the maternal and infant visits must be coordinated such that breast milk, maternal blood and infant blood are all collected within a ninety-minute period. For all other infants, data may be abstracted from the participant chart at any point that it is available within the allowable window for the visit.

Maternal 16-24 Weeks Visit Procedures (Component 4)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medications history since last visit per <a href="#">Sections 6.6</a> and <a href="#">10.3</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> <li>• Single PK sample (breast milk transfer PK) per <a href="#">Section 6.10.4*</a></li> </ul>
	Breast milk	Collect breast milk for: <ul style="list-style-type: none"> <li>• Breast milk transfer PK per <a href="#">Section 6.10.4*</a></li> </ul>

Infant 16-24 Weeks Visit Procedures (Component 4)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medication and feeding history since last visit per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	<i>For infants undergoing breast milk transfer PK sampling, collect blood for:</i> <ul style="list-style-type: none"> <li>• Breast milk transfer PK sample per <a href="#">Section 6.10.4*</a></li> </ul>

\* Maternal blood, breast milk, and infant blood must be all be collected within ninety minutes of the first of these three samples that is drawn.

## 6.5 Component 5 Study Visits and Procedures

### 6.5.1 Screening Procedures (Component 5)

Refer to [Section 4.7](#) for a description of the study recruitment, screening and enrollment process.

Screening procedures may be performed within 60 days prior to enrollment, up to and including the day of enrollment. Participants (mother-infant pairs) must provide consent before any activities are performed to determine eligibility. For potential participants who do not meet the eligibility criteria, screening should be discontinued once ineligibility is determined. Final eligibility determination and confirmation must precede enrollment.

Screening Procedures (Component 5) (Within 60 days prior to enrollment)		
Administrative and Regulatory		<ul style="list-style-type: none"> <li>• Obtain written informed consent/assent</li> <li>• Assign PIDs to mother and infant</li> <li>• Obtain available documentation of mother's HIV status</li> </ul>
Clinical		<ul style="list-style-type: none"> <li>• Assess documentation of HIV infection in relation to study requirements</li> <li>• Obtain available medical records and medical and medication history</li> <li>• Assess ARV drug history in relation to study requirements</li> <li>• Assess breastfeeding intentions in relation to study requirements</li> </ul>
Laboratory		Collect blood for: <ul style="list-style-type: none"> <li>• Confirmatory HIV testing (<i>if needed per <a href="#">Section 4.5</a></i>)</li> </ul>

### 6.5.2 Entry/Maternal 5-9 Days and Infant 5-9 Days Visits (Component 5)

Refer to [Section 4.7](#) for a description of the study recruitment, screening and enrollment process.

Entry must occur at the 5-9 Days visit within 5 and 9 days after delivery/birth. The day of delivery/birth is defined as Day 0 and all follow-up visits are scheduled from this date. Procedures that may provide information relevant to eligibility for the study should be performed first, prior to final eligibility determination. Final eligibility determination must precede enrollment. In the event that a mother-infant pair is found to ineligible on the day of enrollment, enrollment should not occur. Sites should make every effort to plan participant enrollment and initial PK sampling procedures on the same day; however, initial PK sampling must occur within the window for the visit.

The maternal and infant visits must be coordinated such that breast milk, maternal blood and infant blood are all collected within a ninety-minute period per [Section 6.10.4](#). On any given PK sampling day, the visit should only be conducted if the mother-infant pair meet the requirements for breast milk transfer sampling per [Section 6.10.4](#).

<b>Maternal Entry/5-9 Days Visit Procedures (Component 5)</b>		
<b>Administrative and Regulatory</b>		<ul style="list-style-type: none"> <li>• Complete final eligibility determination and confirmation (Entry visit only, prior to enrollment)</li> <li>• Complete paper-based eligibility checklist (prior to enrollment), enter checklist data into SES to enroll the mother-infant pair, print and file a copy of the confirmation file (Entry visit only)</li> </ul>
<b>Clinical</b>		<ul style="list-style-type: none"> <li>• Obtain medical and medications history per <a href="#">Sections 6.6</a> and <a href="#">10.3</a> (at Entry Visit, perform prior to enrollment)</li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events (at 5-9 Days Visit only for participants who completed Entry visit prior)</li> </ul>
<b>Laboratory</b>	<b>Blood</b>	Collect blood for: <ul style="list-style-type: none"> <li>• Single PK sample per <a href="#">Section 6.10.4</a>*</li> </ul> <i>For women who have consented for genetic testing:</i> <ul style="list-style-type: none"> <li>• Store DBS for pharmacogenetics: Obtain from whole blood PK sample</li> </ul>
	<b>Breast milk</b>	Collect breast milk for: <ul style="list-style-type: none"> <li>• Breast milk transfer PK per <a href="#">Section 6.10.4</a>*</li> </ul>

<b>Infant Entry/5-9 Days Visit Procedures (Component 5)</b>		
<b>Administrative and Regulatory</b>		<ul style="list-style-type: none"> <li>• Complete final eligibility determination and confirmation (Entry visit only, prior to enrollment)</li> <li>• Complete paper-based eligibility checklist (prior to enrollment), enter checklist data into SES to enroll the mother-infant pair, print and file a copy of the confirmation file (Entry visit only)</li> </ul>
<b>Clinical</b>		<ul style="list-style-type: none"> <li>• Obtain medical and medication and feeding history since birth per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events (at 5-9 Days Visit only for participants who completed Entry visit prior)</li> </ul>
<b>Laboratory</b>	<b>Blood</b>	Collect blood for: <ul style="list-style-type: none"> <li>• Breast milk transfer PK sample per <a href="#">Section 6.10.4</a>*</li> <li>• <i>For infants for whom informed consent for genetic testing has also been obtained, DBS storage for pharmacogenetics</i></li> </ul>

\* Maternal blood, breast milk, and infant blood must be all be collected within ninety minutes of the first of these three samples that is drawn

### 6.5.3 Maternal 2-12 Weeks and Infant 2-12 Weeks Visits (Component 5)

The maternal and infant 2-12 Weeks visit must take place within 14 and 90 days after delivery/birth.

The maternal and infant visits must be coordinated such that breast milk, maternal blood and infant blood are all collected within a ninety-minute period per [Section 6.10.4](#).

Maternal 2-12 Weeks Visit Procedures (Component 5)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medications history since last visit (per <a href="#">Sections 6.6</a> and <a href="#">10.3</a>)</li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> <li>• Single PK sample per <a href="#">Section 6.10.4*</a></li> <li>•</li> </ul>
	Breast milk	Collect breast milk for: <ul style="list-style-type: none"> <li>• Breast milk transfer PK per <a href="#">Section 6.10.4*</a></li> </ul>

Infant 2-12 Weeks (Component 5)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medication and feeding history since last visit per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> <li>• Breast milk transfer PK sample per <a href="#">Section 6.10.4*</a></li> </ul>

\* Maternal blood, breast milk, and infant blood must be all be collected within ninety minutes of the first of these three samples that is drawn

#### 6.5.4 Maternal 16-24 Weeks and Infant 16-24 Weeks Visits (Component 5)

The maternal and infant 16-24 Weeks visit must take place within 112 and 174 days after delivery/birth.

The maternal and infant visits must be coordinated such that breast milk, maternal blood and infant blood are all collected within a ninety-minute period per [Section 6.10.4](#).

Maternal 16-24 Weeks Visit Procedures (Component 5)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medications history since last visit (per <a href="#">Sections 6.6</a> and <a href="#">10.3</a>)</li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> <li>• Single PK sample per <a href="#">Section 6.10.4*</a></li> <li>•</li> </ul>
	Breast milk	Collect breast milk for: <ul style="list-style-type: none"> <li>• Breast milk transfer PK per <a href="#">Section 6.10.4*</a></li> </ul>

Infant 16-24 Weeks Visit Procedures (Component 5)		
Clinical		<ul style="list-style-type: none"> <li>• Update medical and medication and feeding history since last visit per <a href="#">Section 6.9</a></li> <li>• Perform abbreviated physical exam</li> <li>• Identify/review/update adverse events</li> </ul>
Laboratory	Blood	Collect blood for: <ul style="list-style-type: none"> <li>• Breast milk transfer plasma PK sample per <a href="#">Section 6.10.4*</a></li> </ul>

\* Maternal blood, breast milk, and infant blood must be all be collected within ninety minutes of the first of these three samples that is drawn.



## 6.6 Maternal Medical and Medication History

Collection of medical and medication history information is required at each scheduled visit as indicated in the SoEs. A baseline history is established at entry, and interval (since the last visit) histories are obtained at subsequent follow-up visits. All history information may be obtained based on participant self-report, but available medical records should also be obtained when possible to supplement self-reported information.

Documented medical conditions will be assessed for severity as described in [Section 7.3.3](#), and new conditions occurring during follow-up will also be assessed for relationship to the drug under study as described in [Section 8](#). Relevant dates will be recorded for all conditions and medications.

[Table 4](#) specifies the **minimum** baseline and interval medical and medications history elements and other clinical and laboratory evaluations that must be source documented for maternal participants, as well as associated eCRF entry requirements. Baseline eCRFs are to be completed at Entry. Abnormal findings identified prior to enrollment will be entered into medical history eCRFs, and abnormal findings identified after enrollment will be entered into adverse events eCRFs, as specified in [Section 7.2](#). All drugs under study, as well as all concomitant medications, will be recorded on Medication Log eCRFs. Laboratory test results will be recorded on laboratory eCRFs as specified in [Table 4](#) and [Section 7.2.3](#).

**Table 4. Documentation Requirements for Maternal Medical and Medications History**

<b>Evaluation</b>	<b>Component</b>	<b>Assess for, Source Document and Enter into eCRF</b>	
<b>Baseline Maternal Evaluations</b>			
<b>Evaluation</b>	<b>Component</b>	<b>Assess for and Source Document</b>	<b>Enter into eCRFs</b>
Demographics	All Components	Date of birth and other socio-demographics (Note: to be entered into Eligibility Checklist at enrollment, not eCRF)	All
Medication History	Component 1 Component 2 Component 3 Component 4	All medications (other than ARVs, but including TB treatment drugs) taken or administered during the current pregnancy, that meet the following criteria: <ul style="list-style-type: none"> <li>• All prescription medications</li> <li>• Blood products and transfusions</li> <li>• Prenatal vitamins</li> <li>• Women on integrase inhibitors only: Cation-containing antacids, acid suppressants, and iron supplements</li> </ul>	All
	Component 5	All medications (including ARVs) taken or administered within 30 days prior to enrollment and/or ongoing at enrollment, that meet the following criteria: <ul style="list-style-type: none"> <li>• All prescription medications, including those given in the intrapartum/postpartum period, but excluding labor and delivery anesthesia/epidurals</li> <li>• Blood products and transfusions</li> <li>• Prenatal vitamins</li> </ul>	All
ARV Medication History	Component 1 Component 3 Component 4	Any ARV medications received in the 12 months prior to the estimated date of delivery, including all current ARV medications (including start/stop dates)	All
	Component 2	Any ARV medications (including for treatment <u>or</u> prevention of HIV) received in the 12 months prior to the estimated date of delivery (including injection administration dates)	All
TB Medication History	Component 4	Any second-line TB medication taken or administered in the 24 months prior to the estimated date of delivery	All
Medical History	Component 1 Component 2 Component 3 Component 4	All medical conditions occurring within the current pregnancy or ongoing at the time of enrollment.	All conditions that meet the criteria for pre-existing conditions in <a href="#">Section 7.2.1</a> .

Evaluation	Component	Assess for, Source Document and Enter into eCRF	
	Component 5	All medical conditions occurring within 30 days prior to enrollment and/or ongoing at enrollment.	All conditions that meet the criteria for pre-existing conditions in <a href="#">Section 7.2.1</a> .
Electrocardiogram (ECG)	Component 4	<i>For women taking BDQ, CFZ, and/or DLM only:</i> Most recent ECG result available in medical records within 6 months prior to entry	All
Laboratory Test Results	Components 1-4	All of the following laboratory test results during the <u>current pregnancy</u> that are available in medical records: <ul style="list-style-type: none"> <li>• Grade 2 or higher AST, ALT, albumin, BUN, creatinine, and bilirubin</li> <li>• Grade 2 or higher CBC</li> <li>• <i>Components 3 and 4 only:</i> Grade 2 or higher ANC</li> <li>• <i>Component 4 only:</i> Electrolytes (potassium, magnesium, calcium)</li> </ul>	All
	Component 5	All of the following laboratory test results within <u>30 days prior to enrollment</u> that are available in medical records: <ul style="list-style-type: none"> <li>• AST, ALT, BUN, creatinine, and bilirubin</li> <li>• CBC</li> </ul>	All
HIV Infection History	Component 1 Component 2 Component 3 Component 4	<ul style="list-style-type: none"> <li>• HIV infection status at Entry</li> <li>• History of any ongoing major HIV-related diagnoses</li> <li>• All HIV-1 RNA results and Lymphocyte subsets available in medical records during the current pregnancy (WLHIV only)</li> </ul>	All
	Component 5	<ul style="list-style-type: none"> <li>• HIV infection status at Entry</li> <li>• History of any major HIV-related diagnoses within 30 days prior to enrollment</li> <li>• All HIV-1 RNA results and Lymphocyte subsets available in medical records within 30 days prior to enrollment (WLHIV only)</li> </ul>	All
TB History	Component 3 Component 4	Lifetime history of all TB diagnoses	All

<b>Evaluation</b>	<b>Component</b>	<b>Assess for, Source Document and Enter into eCRF</b>	
Obstetrical History	Component 1 Component 2 Component 3 Component 4	Obstetrical History: <ul style="list-style-type: none"> <li>• Pre-pregnancy weight (current pregnancy only)</li> <li>• Lifetime history of major obstetrical diagnoses, including during the current pregnancy</li> </ul>	All
	Component 5	Obstetrical History: <ul style="list-style-type: none"> <li>• Pre-pregnancy weight (most recent pregnancy only)</li> <li>• History of major obstetrical diagnoses within 30 days prior to enrollment</li> <li>• Pregnancy outcomes of most recent pregnancy</li> <li>• Most recent labor and delivery records</li> </ul>	All
Eligibility criteria	All Components	Any other information needed to determine eligibility for the study (assess for and source document if no associated eCRFs)	All (as appropriate)
<b>Interval Maternal Evaluations</b>			
Concomitant Medications	All Components	Modifications to concomitant medications ongoing at the last study visit, and use of any new concomitant medications since the last study visit that meet the following criteria: <ul style="list-style-type: none"> <li>○ All prescription medications, including those given in the intrapartum/postpartum period, but excluding labor and delivery anesthesia/epidurals</li> <li>○ Blood products and transfusions</li> <li>○ Prenatal vitamins</li> <li>○ Women on integrase inhibitors only: Cation-containing antacids, acid suppressants, and iron supplements</li> </ul>	All
Drugs Under Study	All Components	All modifications to the drugs under study since the last visit, including treatment initiations, modifications, and permanent discontinuations, as well as any drug under study use in the intrapartum period.	All
Medical Conditions	All Components	Current status of any medical conditions that were ongoing at the previous visit, and occurrence of any new conditions (signs, symptoms, illnesses, and other diagnoses) since the last study visit.	All conditions that meet the criteria for adverse events reporting in <a href="#">Section 7.2.2.</a>
ECG	Component 4	<i>For women taking BDQ, CFZ, and/or DLM only:</i> All ECG results available in medical records since the last study visit	All
Laboratory Test Results	Component 5	All of the following laboratory test results available in medical records since the last study visit:	All

Evaluation	Component	Assess for, Source Document and Enter into eCRF	
		<ul style="list-style-type: none"> <li>• AST, ALT, BUN, creatinine, and bilirubin</li> <li>• CBC</li> <li>• HIV-1 RNA results</li> </ul>	
Obstetrical History	Component 1 Component 2 Component 3 Component 4	Any updates to obstetrical history since the last study visit, including: <ul style="list-style-type: none"> <li>• Pregnancy outcome</li> <li>• Labor and delivery record</li> </ul>	All

In addition to the above, PK data will also be source documented and entered into eCRFs as described in [Section 10.3](#).

## 6.7 Maternal Physical Examinations

Vital signs will be evaluated at all scheduled maternal visits as follows:

- Height at entry only
- Weight at all scheduled visits
- Blood pressure at all scheduled visits
- Temperature at all scheduled visits
- Pulse rate at all scheduled visits

All of the above should be source documented and entered into eCRFs.

At all visits, additional physical evaluations may be performed at the discretion of the site investigator. For example, body systems may be examined based on previously- and newly-reported signs, symptoms, or diagnoses. The findings of all such evaluations should be source documented. Abnormal findings identified prior to enrollment will be entered into medical history eCRFs if applicable per [Section 7.2](#); abnormal findings identified after enrollment will be entered into adverse event eCRFs if applicable per [Section 7.2](#).

## 6.8 Infant Physical Examination

Infant measurements will be evaluated at all scheduled infant visits as follows:

- Length at all scheduled visits
- Weight at all scheduled visits

All of the above should be source documented and entered into eCRFs.

At all visits, additional physical evaluations may be performed at the discretion of the site investigator. For example, body systems may be examined based on previously- and newly-reported signs, symptoms, or diagnoses. The findings of all such evaluations should be source documented. Abnormal findings identified prior to enrollment (applicable to Component 5 infants only) will be entered into medical history eCRFs if applicable per [Section 7.2](#); abnormal findings identified after enrollment will be entered into adverse event eCRFs if applicable per [Section 7.2](#).

## 6.9 Infant Medical, Medication, and Feeding History

### 6.9.1 Infant Medical and Medication History

Collection of medical and medication history information is required at each scheduled infant visit. A baseline history is established at the first study visit after birth and interval (since the last visit) histories are obtained at subsequent follow-up visits. Infant birth details should ideally be obtained from available medical records. If birth details are not available, indicate as such on the eCRF. Thereafter, history information may be obtained based on maternal report and/or chart abstraction. See [Table 5](#) in [Section 6.9.3](#) for source documentation and eCRF requirements.

### 6.9.2 Infant Feeding History

An infant feeding history is required at each scheduled infant visit as indicated in the Schedules of Evaluations. See [Table 5](#) in [Section 6.9.3](#) for source documentation and eCRF requirements.

### 6.9.3 Summary of Infant Data to be Collected

Table 5 summarizes the data that should be collected, source documented and entered into eCRFs for each of the Infant visits.

**Table 5. Documentation Requirements for Infant History**

Element	Assess for, Source Document and Enter into eCRF
<b>Baseline</b>	
Medical and Medication History	<p>Obtain from available medical records:</p> <ul style="list-style-type: none"> <li>• Date and time of birth</li> <li>• Sex</li> <li>• Estimated gestational age at birth (by best available method)</li> <li>• Birth length and weight</li> <li>• Any medical conditions identified since birth that meet the criteria in <a href="#">Section 7.2</a></li> <li>• All prescription medications taken or administered since birth</li> <li>• <i>For infants of mothers taking BDQ, CFZ, and/or DLM:</i> All ECG results available since birth</li> <li>• Laboratory results available in medical records:               <ul style="list-style-type: none"> <li>— <i>For infants of WLHIV:</i> All HIV test results</li> <li>— Hematology: All Grade 2 or higher results for CBC with differential and platelets; first and last results at each reportable grade and first normal result afterward.</li> <li>— Chemistries: All Grade 2 or higher glucose, AST, and ALT results.</li> <li>— <i>For HIV-infected infants only:</i> Grade 2 or higher electrolytes, BUN, creatinine, total and direct bilirubin, lipase, albumin, total protein, triglycerides, cholesterol, creatinine phosphokinase (CPK), and amylase results.</li> </ul> </li> </ul>
Feeding History	<ul style="list-style-type: none"> <li>• Feeding method: formula or breast milk</li> <li>• Date and time of first breastfeeding, if applicable</li> <li>• Date and time of last exposure to breast milk, if applicable</li> </ul>
<b>Interval</b>	
Medical and Medication History	<ul style="list-style-type: none"> <li>• Current status of conditions that were ongoing at the previous visit</li> <li>• Current status of prescription medications that were ongoing at the previous visit</li> <li>• Occurrence of any new conditions identified since the last visit that meet the criteria in <a href="#">Section 7.2</a></li> <li>• Use of any new prescription medications since the last visit</li> <li>• <i>For infants of mothers taking BDQ, CFZ, and/or DLM:</i> All ECG results</li> <li>• Laboratory results available in medical records since the last study visit:               <ul style="list-style-type: none"> <li>— <i>For infants of WLHIV:</i> All HIV test results</li> <li>— Hematology: All Grade 2 or higher results for CBC with differential and platelets; first and last results at each reportable grade and first normal result afterward.</li> <li>— Chemistries: All Grade 2 or higher glucose, AST, and ALT results.</li> <li>— <i>For HIV-infected infants only:</i> Grade 2 or higher electrolytes, BUN, creatinine, total and direct bilirubin, lipase, albumin, total protein, triglycerides, cholesterol, creatinine phosphokinase (CPK), and amylase results.</li> </ul> </li> </ul>
Feeding History	<ul style="list-style-type: none"> <li>• Feeding method since last visit: formula or breast milk</li> <li>• Date and time of last exposure to breast milk, if applicable</li> </ul>

## 6.10 Maternal and Infant PK Sampling Procedures

PK sampling will be conducted at visits as indicated in the component-specific schedules of evaluations. [Sections 6.10.1](#) through [6.10.4](#) describe PK sampling procedures. Refer to [Section 10](#) for more details on PK design, data collection and analysis. Refer to the IMPAACT 2026 Laboratory Processing Chart (LPC) for collection, processing, and shipping instructions for PK samples.

### 6.10.1 Maternal Intensive and Sparse PK Sampling Procedures: Components 1, 3, and 4

Women in Components 1, 3, and 4 will undergo intensive and/or sparse PK sampling at visits as indicated in their respective SoEs. Specific intensive or sparse PK sampling schedules to be used for each drug and their corresponding time points and blood volumes are presented in [Appendix IV](#). Intensive PK will consist of repeat blood sampling to determine plasma drug concentration levels; sparse PK will consist of repeat blood sampling with storage of plasma, DBS and PBMC to determine intracellular TAF concentrations and will be done for TAF arms only (Arms 1.3, 1.4 and 1.5). Specific processing instructions for samples at each time point are detailed in the LPC.

In preparation for an intensive or sparse PK sampling visit, sites may contact participants or parents/guardians to reinforce adherence. Specifically, the timing of dosing of the drug(s) under study – whether dosed once or twice a day or whether ARV, TB treatment drugs, or a combination -- for the three days prior to and the day of the PK evaluation must be approximately the same time of day and must be approximately the same for the PK evaluation(s) (i.e. if timing of dosing needs to be changed to facilitate PK sampling, this must be done at least three days prior to PK sampling day). For example, a drug must be taken in the morning for three days in a row and on the morning of the PK sampling day. If a dose is taken in the evening during the three-day period, then the visit would have to be rescheduled. On each maternal PK sampling day, the study visit should be scheduled to start at the point in time that coincides with the end of the previous dosing interval.

If a missed dose is reported within the three days prior to an intensive or sparse PK sampling visit, the visit should be rescheduled within the visit window. For participants who report intercurrent illness immediately prior to the day of the scheduled PK visit that may interfere with study product administration or result in malabsorption of study product (e.g., fever, vomiting, diarrhea), the PK evaluation should be rescheduled. For participants whose treatment has been interrupted for more than one day, sites should contact the Core Protocol Team for guidance related to scheduling the PK sampling visit. For participants whose treatment has been discontinued, see [Section 6.13](#).

Additional guidance for sequencing of procedures at Component 1, 3, or 4 visits where intensive and/or sparse PK sampling procedures are conducted are as follows:

- Pre-dose PK blood sample must precede ingestion of the drug(s) under study.
- The dose(s) of the drug(s) under study will be administered on site after the pre-dose sample is drawn. An intravenous catheter will be placed in an arm vein for serial blood collection. Refer to [Section 5.2](#) for additional guidance on administration of drugs under study.



- For women having intensive PK sampling for multiple drugs under study, doses of drugs under study should be administered at the same time or within a 15-minute window on either side of the first dose taken. If doses are staggered more than 15 minutes apart on either side of the first dose, additional samples must be drawn to complete the PK evaluations for EACH drug taken outside of the 15-minutes on either side of the first dose window (i.e. samples need to be drawn at 1, 2, 4, etc. hours post-dose for each drug under study if doses are staggered more than 15 minutes apart on either side of the first dose).
- Women on a TAF-containing regimen undergoing sparse PK sampling for intracellular ARV assessments and who are also undergoing intensive PK assessments for other ARV medications will have the sparse sampling collection during the intensive PK sampling.
- Participants having 12-hour sampling should ideally remain in the clinic until the completion of PK sampling. Participants having 24-hour sampling may leave the clinic following the 3-hour (sparse PK) or 12-hour (intensive PK) time point and return for the 24-hour time point.

The oral dose dates, times, dose amounts, and food intake around the doses must be source documented and entered into eCRFs for the doses observed at PK visits, in addition to the previous **two doses**, per [Section 10.3](#).

### 6.10.2 Maternal Delivery and Cord Blood PK Sampling Procedures: Components 1, 2, 3, and 4

Transplacental passage of the ARV and TB treatment drugs under study will be assessed by measurement of drug concentrations in maternal plasma at the time of delivery and in cord blood. A maternal single random PK sample will be drawn at the time the cord is clamped. A single random PK sample will also be obtained from the umbilical cord, immediately after the cord is clamped. Plasma will be stored from all samples. A DBS will also be stored for women on Arms 1.3, 1.4, and 1.5 (TAF arms) from the maternal and cord blood sample; additionally, if adequate blood volume is obtained, if personnel are available for processing, and if circumstances permit, PBMCs should also be isolated from maternal and cord blood samples for women on Arms 1.3, 1.4, and 1.5 only. Collection of cord blood and maternal delivery sample can be omitted if there are circumstances that prohibit collection (i.e. delivery at non-study facility, delivery during non-business hours). For Component 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.

### 6.10.3 Infant Washout PK Sampling: Components 1, 2, 3, and 4

Infants must meet the following requirements to undergo washout PK sampling:

- Birth weight > 1000 grams.
- Not receiving disallowed medications described in [Section 5.4](#).
- No severe congenital malformations or other medical conditions incompatible with life or that would interfere with study participation or interpretation, as judged by the site investigator.
- Components 1, 3 and 4 only: Mother is still receiving the drug under study at the time of delivery and has not missed two or more doses prior to delivery.

Infants who meet the above requirements will have blood samples collected as follows:

Visit/Window	Birth Visit			5-9 Days	12-16 Days (Component 2 only)
	2-10 hrs	18-28 hrs	36-72 hrs		
Maximum Blood Volume	0.75 mL	0.75 mL	0.75 mL	0.75 mL	0.75 mL

DBS will also be processed from each whole blood sample for infants on Arms 1.3, 1.4, and 1.5 (TAF arms) for intracellular TAF assessments.

Collection of infant PK samples can be omitted, with approval of the Core Protocol Team, if there are circumstances that prohibit collection (i.e. delivery at a non-study facility, delivery during non-business hours).

#### 6.10.4 Mother-Infant Pair Breast Milk Transfer PK Sampling: Components 2, 3, 4 and 5

Select arms of Components 2, 3, 4, and 5 will include breast milk transfer PK sampling for mother-infant pairs. Specifically, breast milk transfer PK sampling will be performed in the following study arms: 2.1, 3.2, 3.3, 4.1, and all Component 5 arms. Additionally, among these arms, sites where breastfeeding is not standard of care may opt to omit breast milk transfer PK sampling and must modify their site-specific informed consent forms appropriately. For sites that do not opt out of breast milk transfer PK sampling, mothers and their infants must meet the following requirements at each visit to undergo breast milk transfer sampling:

- Mother-infant pair are breastfeeding at the time of the breast milk PK sampling visit.
- Components 3, 4 and 5 only: Mother is still receiving the drug(s) under study at the time of the breast milk PK sampling visit and has not missed a dose within three days prior to the visit.
- Infant meets the following requirements:
  - a. Birth weight > 1000 grams.
  - b. Infant not receiving disallowed medications described in [Section 5.4](#).
  - c. No severe congenital malformations or other medical conditions not compatible with life or that would interfere with study participation or interpretation, as judged by the site investigator.

Mother-infant pairs who do not meet these requirements will not complete visits or procedures that are specific to breast milk transfer PK sampling (i.e. maternal and infant blood and breast milk sampling for breast milk transfer PK).

For visits in which only breast milk transfer PK sampling is being performed, the drug under study can be administered off-site or on-site on the day of the breast milk transfer PK sampling visit. The date, time, and amount of the doses, and food intake around the doses must be source documented and entered into eCRFs for the **three doses** prior to the breast milk transfer PK sampling visit (included doses taken on the day of the visit), per [Section 10.3](#). For visits where intensive or sparse PK sampling is also being performed, the drug under study will be administered on-site, per [Section 6.10.1](#). If a missed dose is reported within the three days prior to a breast milk transfer PK sampling visit, the visit should be rescheduled within the visit window. In preparation for a breast milk transfer PK sampling visit, sites may contact participants or parents/guardians to reinforce adherence.

Breast milk transfer PK sampling is comprised of three single samples collected in parallel: maternal blood, breast milk, and infant blood. Plasma will be stored from all blood samples. The collection of the three samples must be as follows:

- At visits where intensive or sparse PK sampling is not also indicated (i.e., *only* breast milk PK and/or infant washout PK sampling are being performed): the maternal blood, breast milk and infant blood samples must be all collected within ninety minutes of the first sample drawn.
- At visits where intensive PK sampling is also indicated: the breast milk sample and infant blood sample (applicable to infant washout PK sample if infant washout PK sampling is being performed at the visit) must be collected within ninety minutes of the maternal 2-hour post-dose intensive PK sample. A separate maternal blood sample will not be collected at visits where intensive PK sampling is performed, as the drug concentration in maternal blood will be measured from the intensive PK sample. Likewise, for infants, if washout PK sampling is being performed, an additional infant blood sample will not be collected specifically for breast milk transfer PK as the drug concentration in infant blood will be measured from the infant washout PK sample.

## 6.11 Maternal and Infant Pharmacogenetics: All Components

Informed consent or assent (as applicable) will be requested for optional pharmacogenetic testing for maternal participants and their infants. For mothers for whom informed consent or assent (as applicable) is obtained, DBS will be prepared for this testing once, from the volume of blood collected at the initial PK sampling as indicated in the SOE (an additional sample is not required for mothers). For infants for whom informed consent is obtained, who ALSO meet requirements for infant washout PK sampling (Components 1-4) or breast milk transfer PK sampling (Component 5), blood will be collected, and DBS will be prepared for this testing once, at either the Birth visit or 5-9 Days visit (an additional sample is required for infants). Refer to the LPC for detailed collection, processing and shipping instructions.

## 6.12 Additional Considerations for Laboratory Procedures

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at:

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

### 6.12.1 Specimen Collection

Specimens will be collected for this study as indicated in the component-specific SOEs and per detailed guidance provided in the LPC, which will be available on the study-specific webpage at: <http://impaactnetwork.org/studies/IMPAACT2026.asp>.

In accordance with US National Institutes of Health (NIH) recommendations, for participants 18 years of age or older, adult blood collection will not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period. For participants less than 18 years of age, pediatric blood collection will not exceed 5 mL/kg in a single day or 9.5 mL/kg in any eight-week period.

In the event that blood collection must be limited, available specimens should be prioritized for use in the following order for maternal participants: (1) plasma for PK, (2) DBS and PBMC for PK, (3) hematology, (4) chemistry, (5) HIV RNA, (6) CD4 cell count. Available specimens should be prioritized for use in the following order for infant participants: (1) plasma for washout PK, (2) DBS for washout PK, (3) plasma for breast milk PK (4) pharmacogenetics.

### **6.12.2 Specimen Preparation, Testing, Storage, and Shipping**

All specimens collected for this study will be labeled, transported, processed, tested, stored and/or shipped in accordance with the DAIDS policy referenced in [Section 6.12](#), site and local laboratory SOPs, and the LPC. The frequency of specimen collection will be directed by the component-specific Schedules of Evaluations. Refer to [Section 10.4](#) for additional instruction related to PK specimens shipping. The Laboratory Data Management System (LDMS) will be used to document specimen collection, testing, storage, and shipping as specified in LPC.

HIV-1 RNA assays must be performed in a laboratory that is CLIA certified (for U.S. sites) or VQA-certified (for non-U.S. sites) for the assay performed. At least one of the diagnostic tests to confirm HIV-infection per criteria [4.5.3](#) must be performed in a CLIA-certified (for U.S. sites) or VQA-certified (for non-U.S. sites) laboratory. CD4 assays must be performed in a laboratory that is CLIA certified (for U.S. sites) or IQA-certified (for non-U.S. sites) for the assay performed.

### **6.12.3 Biohazard Containment**

Transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood, and blood products. Respiratory pathogens such as Mycobacterium tuberculosis (MTB) are transmitted by inhalation of droplet nuclei. Appropriate blood, secretion, and respiratory precautions will be employed by all personnel in the collection of clinical samples and the shipping and handling of all clinical samples and isolates for this study, as currently recommended by the Centers for Disease Control and Prevention in the United States, the WHO internationally and the National Institutes of Health. All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for United Nations (UN) 3373, Biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for UN 2814 Category A Infectious Substances.

### **6.13 Early Discontinuation or Dose Adjustment of Drug(s) under Study**

Women and their infants in Components 1, 3, and 4 who discontinue or adjust the dose of any of the drug(s) under study after the initial PK sampling visit but prior to completion of follow-up will have no further PK sampling done. These women and their infants will be followed for safety and clinical outcomes throughout the duration of the study follow-up period and will complete all visits and associated procedures per relevant SOE with the exception of PK sampling. Women and their infants in Component 5 who discontinue any of the drug(s) under study after Entry/initial PK sampling visit will no longer meet breast milk transfer PK requirements and will be terminated from the relevant study arm per [Section 4.9](#).

## **7 SAFETY ASSESSMENT, MONITORING, AND REPORTING**

Participant safety will be carefully assessed, monitored, and reported at multiple levels throughout this study. [Section 7](#) describes safety-related roles, responsibilities, and procedures for site investigators. The safety monitoring roles of the Protocol Team and the IMPAACT Study Monitoring Committee (SMC) are briefly referenced in [Section 7.1](#) and described in greater detail in [Section 9.5](#). Unless otherwise noted, the specifications of this section apply to mothers and infants in all study arms.

### **7.1 Safety-Related Roles and Responsibilities**

#### **7.1.1 Site Investigators**

Site investigators are responsible for continuous monitoring of all study participants and for alerting the Protocol Team if unexpected concerns arise. Site investigators will enter safety-related data into eCRFs as indicated in [Section 7.2](#) and complete EAE reporting as indicated in [Section 7.3](#). Site investigators are also responsible for prompt reporting to their IRBs/ECs and other applicable review bodies of any unanticipated problems involving risks to participants or others.

#### **7.1.2 Core Protocol Team**

The following Protocol Team Members comprise the Core Protocol Team: Chair and Vice-Chairs, Medical Officers, Protocol Investigators, Pharmacologists, Statisticians, Data Managers, and Clinical Trial Specialists. The Core Protocol Team will provide guidance as needed regarding all aspects of participant management, including but not limited to questions regarding participant eligibility, management of adverse events (AE), and management of the drug under study. Refer to [Section 8](#) for more information on participant management.

On behalf of the full Protocol Team, the Core Protocol Team will monitor participant safety through routine review of study data reports as described in [Section 9.5.1](#).

#### **7.1.3 Study Monitoring Committee**

An independent IMPAACT SMC will monitor participant safety through routine and as needed reviews of study data. Refer to [Section 9.5.2](#) for more information on the composition and role of the SMC in monitoring of this study.

### **7.2 Safety-Related Data Collection**

The definition of the term adverse event provided in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual) will be used in this study. This definition will be applied to all participants beginning at the time of enrollment, regardless of prior or subsequent administration of or exposure to the drug under study. Any untoward medical conditions (including abnormal laboratory test results, signs, symptoms, or diseases) identified prior to enrollment will be considered pre-existing conditions. Refer to [Section 4.7](#) for more information on defining the effective point of enrollment in the study.

Pre-existing conditions, adverse events and laboratory test results will be entered into eCRFs as specified below in [Sections 7.2.1--7.2.3](#).

## 7.2.1 Pre-Existing Conditions

All pre-existing conditions occurring during the timeframes specified in [Section 6.6](#) (for maternal baseline evaluations) and [6.9](#) (for infant baseline evaluations) that meet the following criteria will be entered into medical history eCRFs.

### Maternal Pre-existing Conditions

- All Grade 3 and higher conditions
- All conditions that meet the definition of serious in Version 2.0 of the DAIDS EAE Manual

### Infant Pre-existing Conditions:

For Component 1-4 infants: Because these infants will be exposed to the drug under study *in utero*, all abnormal conditions identified during and after birth will be considered adverse events. No pre-existing conditions will be entered into eCRFs for Component 1-4 infants.

For Component 5 infants:

- All congenital anomalies and mitochondrial disorders confirmed at or after birth
- All Grade 2 or higher conditions
- All conditions that meet the definition of serious in Version 2.0 of the DAIDS EAE Manual

## 7.2.2 Adverse Events

The following adverse events will be entered into maternal or infant adverse event log eCRFs as described in [Section 6.6](#) (maternal) and [6.9](#) (infant).

### Maternal Adverse Events:

- All Grade 3 and higher adverse events.
- All serious adverse events (SAEs) as defined in Version 2.0 of the DAIDS EAE Manual and all other events that meet criteria for EAE reporting

### Infant Adverse Events:

- All Grade 2 or higher events
- All congenital anomalies and mitochondrial disorders
- All SAEs as defined in Version 2.0 of the DAIDS EAE Manual and all other events that meet criteria for EAE reporting

In addition, for any event assessed as serious as defined in Version 2.0 of the DAIDS EAE Manual due to the event resulting in hospitalization or prolongation of hospitalization, data regarding the hospitalization will be entered into eCRFs.

## 7.2.3 Laboratory Test Results

In addition to the recording specified above, all protocol-specified laboratory test results will be entered into relevant laboratory eCRFs. Additionally, maternal and infant laboratory test results

that are available in medical records from tests conducted outside of the study will be entered into eCRFs as specified in [Section 6.6](#) (maternal) and [6.9](#) (infant).

## **7.3 Expedited Adverse Event (EAE) Reporting**

### **7.3.1 EAE Reporting to DAIDS**

Requirements, definitions, and methods for expedited reporting of adverse events are outlined in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual), which is available on the DAIDS Regulatory Support Center (RSC) website at: <https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids>.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at:

<https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting>

For questions about DAERS, please contact NIAID Clinical Research Management System (CRMS) Support at:

[CRMSSupport@niaid.nih.gov](mailto:CRMSSupport@niaid.nih.gov)

Queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at: [DAIDSRSCSafetyOffice@tech-res.com](mailto:DAIDSRSCSafetyOffice@tech-res.com)

### **7.3.2 EAE Reporting Requirements for this Study**

For both women and infants, the SAE reporting category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. In addition to all SAEs, any grade 4 or higher hepatotoxicity in mothers or infants and any spontaneous abortion or fetal death must be reported in an expedited manner (i.e., as an EAE).

The drugs for which expedited reporting are required are the drugs under study, listed for each Component and Arm in [Table 1](#).

### **7.3.3 Grading Severity of Events (applies to EAEs and all other adverse events)**

For both women and infants, adverse events will be graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated July 2017, which is available on the RSC website at: <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>

For women who enter the study during pregnancy and are followed postpartum, creatinine and creatinine clearance will be graded based on absolute values only and not change from baseline.

*Note: The DAIDS AE Grading Table Parameter for unintentional weight loss excludes postpartum weight loss. Therefore, maternal weight loss will not be graded in this study.*

### 7.3.4 EAE Reporting Period

For both women and infants, the EAE reporting period is the protocol-specified period of follow-up, beginning at the time of enrollment and ending on the date of the final follow-up visit.

After the above-specified period, only suspected unexpected serious adverse reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported if the study staff become aware of such events on a passive basis (e.g., from publicly available information).

## 8 PARTICIPANT MANAGEMENT

All maternal and infant adverse events identified in this study will be source documented in participant research records, consistent with the policies and procedures referenced in [Section 11](#). Among other details, source documentation will include the severity of each event (graded as described in [Section 7.3.3](#)) and its relationship to the drug(s) under study, assessed by the site investigator according to the following categories and definitions:

<b>Related</b>	There is a reasonable possibility that the adverse event may be related to the drug(s) under study.
<b>Not related</b>	There is not a reasonable possibility that the adverse event may be related to the drug(s) under study.

Further standardized guidance on determining whether there is a reasonable possibility of a relationship is available in the DAIDS EAE Manual, referenced in [Section 7.3.1](#) above.

For mothers, relationship should be assessed for each drug under study received (ingested or administered).

For infants, relationship should be assessed for each drug under study received by the mother to which the infant may have been exposed *in utero* or through breastfeeding.

As 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. With respect to IMPAACT 2026 data collection, adverse events should be entered into eCRFs per [Section 7.2](#).

## 9 STATISTICAL CONSIDERATIONS

### 9.1 General Design Issues

This is a Phase IV prospective, open label, non-randomized pharmacokinetic study of prescribed ARV and TB drugs among pregnant and postpartum women living with and without HIV 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 (see [Table 1](#)).



As stated in [Sections 3.1-3.5](#), the target sample size for each arm in Components 1-4 is 25 evaluable mother-infant pairs per arm, and for each arm in Component 5 is 15 mother-infant pairs. Up to 28 (Components 1, 2, 3 and 4) or 15 (Component 5) pairs may be enrolled per arm if needed to achieve the target number of evaluable participants. A participant's data will be deemed unevaluable by a protocol pharmacologist for a specific analysis if they do not have adequate pharmacokinetic evaluations to determine the pharmacokinetic exposure parameter of interest for that analysis (see [Section 9.6.1](#) for details).

The primary objectives are to describe the pharmacokinetics of prescribed ARV and TB drugs in plasma and/or breast milk when used alone or in combination during pregnancy and postpartum, among WLHIV and HIV-uninfected women and their infants. The secondary objectives are to describe maternal and infant safety and clinical outcomes; to compare ARV and TB drug concentrations in plasma from cord blood with those in maternal plasma at the time of delivery; to describe the neonatal elimination of selected ARV drugs acquired across the placenta after maternal dosing during pregnancy; to describe the kinetics of drug transfer of selected ARVs and/or TB treatment drugs from mother to infant via breast milk, and to describe the PK of ARVs in pregnant and postpartum WLHIV on second-line TB treatment drugs in combination with ARVs. Other objectives are to assess plasma protein binding of highly bound ARVs and TB treatment drugs; and to explore genetic sources of variability in ARV and TB drug exposure.

Several of the primary objectives involve comparing pharmacokinetic parameters to those from a suitable control group. The control group data to be used for these comparisons will vary according to the type of drug (ARV or TB drug) and may include (i) historical pharmacokinetic data reported in the literature or from previously-evaluated arms of IMPAACT P1026s or IMPAACT 2026, and/or (ii) postpartum pharmacokinetic data from the same women who were sampled during pregnancy (see [Section 9.6](#) for details on the control groups to be used and comparisons to be made for each type of arm).

Based on data regarding the ARV drugs presently under study, the major concern is that the ARV drug exposure in pregnant women will be lower than that of the non-pregnant population. For the ARV drugs with plasma PK sampling in Components 1 and 3, interim pharmacokinetic exposure monitoring will be implemented which compares each pregnant woman's values to the distribution from a non-pregnant population, to assess whether the dose may be too low (see [Sections 9.5.1](#) for monitoring details and [Section 9.4](#) for power calculations).

The Primary Completion Date (PCD) for this study will be the date on which data collection is complete for all the primary outcome measures.

The IMPAACT 2026 study design is opportunistic in that it enrolls women who are already receiving the drugs under study as part of clinical care or through a research study, but this design has one major limitation, namely that the results may be overly optimistic. Since participants must be stable on the ARV drug/drug combination and/or TB drug combination for at least two weeks prior to PK sampling, the study population will not include women who started the drug under study and discontinued it within two weeks due to toxicity, intolerance, virologic failure, or any other reason. Thus, this study will not be able to identify pharmacokinetic, safety, or tolerance issues that occur very soon after drug initiation and estimates of the frequency of adverse outcomes may be overly optimistic. The fact that the results of this study will generalize only to the population of women who are able to stay on the drugs under study for at least two weeks will be discussed as a limitation of the study in presentations and publications of results.

The protocol team acknowledges this limitation but feels that the PK data obtained using the current design will still be quite valuable nonetheless.

An integral part of this study is reporting ARV drug assay results for selected study arms to the clinical caregivers of the participants in real time (see [Section 10.4.2](#)). Knowledge of these results may impact which participants complete the sampling protocol without an ARV dosing change and which participants receive an ARV dosing change and need to be replaced. In this way the replacement of unevaluable participants may introduce a selection bias into the population available for the within participant comparison of the pregnant and non-pregnant condition. This potential bias is an inescapable consequence of the study design but is outweighed by the ethical imperative to provide all potentially valuable clinical information to study participants.

## 9.2 Outcome Measures

*Note: The numbering of the outcome measures in this section corresponds to the numbering of the objectives in [Section 2](#).*

Primary and secondary outcome measures listed below in [Sections 9.2.1](#) and [9.2.2](#) of [Table 6](#) will be addressed in the study's primary Statistical Analysis Plan, which will define the content of the Primary Analysis Report (s) (as noted in [Section 9.1](#), there may be more than one Primary Analysis Report if study arms enroll at different rates). This(ese) report(s) will form the basis for the primary manuscript(s) and results reporting to ClinicalTrials.gov. Outcomes of interest for other objectives intended for subsequent publications are listed under "Other Outcome Measures".

**Table 6. Outcome Measures**

<b>Primary Outcome Measures</b>	
<b>9.2.1.1</b>	• See Section 10.2.1.1
<b>9.2.1.2</b>	• See Section 10.2.1.2
<b>9.2.1.3</b>	• See Section 10.2.1.3
<b>9.2.1.4</b>	• See Section 10.2.1.4
<b>9.2.1.5</b>	• See Section 10.2.1.5
<b>Secondary Outcome Measures</b>	
<b>9.2.2.1</b>	<ul style="list-style-type: none"> <li>• Grade 3 or higher maternal adverse events</li> <li>• Grade 2 or higher infant adverse events</li> <li>• Maternal and infant serious adverse events</li> <li>• Grade 3 or higher maternal adverse events assessed as related to the drug under study</li> <li>• Grade 2 or higher infant adverse events assessed as related to the drug under study</li> <li>• Pregnancy outcome, gestational age at birth, and birth weight</li> <li>• Congenital anomaly or mitochondrial disorder</li> <li>• Infant HIV infection status according to diagnosis per local standard of care</li> <li>• Maternal HIV-1 RNA in the second trimester, third trimester, at delivery, and postpartum</li> </ul>
<b>9.2.2.2</b>	• See Section 10.2.2.2
<b>9.2.2.3</b>	• See Section 10.2.2.3
<b>9.2.2.4</b>	• See Section 10.2.2.4
<b>9.2.2.5</b>	• See Section 10.2.2.5
<b>Other Outcome Measures</b>	
<b>9.2.3.1</b>	• See section 10.2.3.1
<b>9.2.3.2</b>	• Drug exposure as measured by AUC in the second trimester, third trimester, and postpartum (for mothers) or drug concentration (for infants)

### **9.3 Randomization, Stratification, and Enrollment Limits**

There is no randomization or stratification in this study.

The enrollment limits for each arm were determined based on the anticipated percentage unevaluable. The following table ([Table 7](#)) shows the initial and maximum enrollment limits for each Component (as well as the target numbers of evaluable women and infants from [Sections 3.1-3.5](#)):

**Table 7. Enrollment Limits by Component**

Component	Target Evaluable	Initial Enrollment Limit*	Maximum Enrollment Limit
1	25 women	25 mother-infant pairs (with 12 slots reserved for 2 <sup>nd</sup> trimester enrollments)	28 mother-infant pairs
2	25 mother-infant pairs	15 mother-infant pairs	28 mother-infant pairs
3	25 women	25 mother-infant pairs (with 12 slots reserved for 2 <sup>nd</sup> trimester enrollments)	28 mother-infant pairs
4	25 women	25 mother-infant pairs (with 12 slots reserved for 2 <sup>nd</sup> trimester enrollments)	28 mother-infant pairs
5	15 mother-infant pairs	15 mother-infant pairs	15 mother-infant pairs

\*Note: The Core Protocol Team may adjust the enrollment limits for specific arms either upward (up to the maximum specified in this table) or downward; see the text below for details.

For Components 1, 3, and 4, the enrollment limit for each arm will initially be set at 25 women (and their infants), with 12 slots reserved for second trimester enrollments. The Core Protocol Team may increase the enrollment limit of an arm up to the maximum specified in the table above if needed to allow for up to 10% unevaluable, or adjust second and third trimester enrollment limits, to achieve the target number of evaluable women (25 women with evaluable third trimester data and, if possible, at least 12 women with evaluable second trimester PK data, per [Sections 3.1, 3.3, and 3.4](#)) or obtain additional infant washout PK data. The determination of evaluable participants is done by the protocol pharmacologists, and the protocol team will decide whether to restrict enrollment. Additionally, the Core Protocol Team may decide to adjust enrollment limits downward to lower than the target evaluable. For example, this may be done in the case of low enrollment due to unexpected changes to patterns of clinical use of a drug under study, unavailability of 2<sup>nd</sup> trimester participants or budgetary constraints. Changes to enrollment limits will be implemented in the SDMC’s enrollment system and sites will be notified and instructed via email.

For Component 2, the enrollment limit for each arm will initially be set at 15 women and their infants, based on the numbers of women anticipated to become pregnant in two ongoing clinical trials (the only current sources of enrollment to this arm) and current funding levels. The Core Protocol Team will closely monitor enrollment and, if feasible, may increase the enrollment limit (up to the maximum of 28 women, if needed) to achieve the target number of evaluable mother-infant pairs (as stated in [Section 3.2](#), this is defined as women with evaluable delivery PK data and infants with evaluable washout PK data).

For Component 5, the enrollment limit for each arm will be set at 15 mother-infant pairs because it is anticipated that some mother-infant pairs in other IMPAACT 2026 Components will provide breast milk transfer PK data, which will be combined with Component 5 data. As such, the Core Protocol Team may decide to close a Component 5 arm early if sufficient data is obtained when combined with breast milk transfer data from other Component arms.

Refer to [Section 9.6.1](#) for the definition of unevaluable.

## 9.4 Sample Size and Accrual

### 9.4.1 Sample Size

As noted in [Section 9.3](#), the target numbers of evaluable participants per arm for the various Components range from 12 to 25. These targets were selected based on sample size calculations for the comparisons to address the primary objectives of this study. As described in more detail in [Section 9.6](#), the data analyses to address the primary objectives vary between Components and only some involve comparisons. For the plasma PK arms for Components 1, 3, and 4, the data analyses to address the primary objectives will include comparisons of antepartum antiretroviral exposure with a target derived from non-pregnant historical control data and also within-participant comparisons of the PK parameter of interest between two conditions (pregnant vs. non-pregnant, or second vs. third trimester); sample size calculations were performed for each type of comparison. For the other arms (Component 1 intracellular arms, Components 2, and 5), the data analyses for the primary objectives will only involve descriptive statistics for the PK parameter of interest at specified time points and the selected sample sizes for the comparisons above are anticipated to provide adequate precision.

For Component 1 and 3, sample size calculations were performed to indicate the ability of the study to assess whether the prescribed dosing regimens for the drugs under study produce adequate drug exposure during pregnancy as compared to historical data from non-pregnant adults (this analysis is called the Stage 1 analysis in [Section 9.6](#)). Such observations will be assessed to determine, if possible, whether the level of exposure to these drugs during pregnancy is adequate, or inadequate, based upon current knowledge.

The PK exposure parameter of primary interest for these sample size calculations is the AUC in plasma (for all ARVs except TAF) and intracellular concentrations of TFV and metabolites (for TAF), as determined from 12-hour sampling or 24-hour sampling (refer to [Appendix IV](#) for the sampling schedule for each drug). The AUC is commonly analyzed as following a log-normal distribution.

The actual sample size will be based on the determination of PK exposure parameters, and whether or not the current dose provides adequate drug exposure to pregnant women. Based on data regarding drugs presently under study, the major concern is that the drug exposure in pregnant women might be lower than that seen in the non-pregnant population. For the ARV drugs with plasma PK sampling in Components 1 and 3, interim pharmacokinetic exposure monitoring will be implemented which compares each pregnant woman's values to the distribution from a non-pregnant population, so that the question of whether the dose is too low will be tested by comparison to historic controls (see [Sections 9.5.1](#) for monitoring details). Adequate exposure will be defined as fewer than 6 out of 25 evaluable pregnant women having PK exposure parameters below the 10<sup>th</sup> percentile for the non-pregnant population, because the protocol team considers that having more than 20% of the women below the 10<sup>th</sup> percentile would be unacceptable. Consequently, if 6 or more of the pregnant women have PK exposure parameters below the 10<sup>th</sup> percentile, it will be concluded that the PK exposure in the pregnant population is lower than that of non-pregnant population. Given the discrete nature of the data, if 6 or more participants have low PK exposure parameters, the lowest sample probability that can be achieved is 24%, 6 out of 25, and the exact 80% confidence limits are (13%, 38%). These confidence limits exclude the tenth percentile and indicate that the protocol team is at least 90%

confident that the true percentage of pregnant women having PK parameters below the 10<sup>th</sup> percentile for the non-pregnant population is greater than 10%. Note that the 10<sup>th</sup> percentile from the non-pregnant historic controls is being treated as a constant.

Table 8 provides the probability of concluding that the exposure of the pregnant population is lower than that of the non-pregnant population given the current dose with a sample size of 25 evaluable women, assuming that the number of pregnant women falling below target is a binomial random variable with success probability equal to the true cumulative probability in the pregnant population of having below-target exposure. Consider four possible true cumulative probabilities in the pregnant population for the value of the 10<sup>th</sup> percentile from the non-pregnant population. If the true cumulative probability corresponds to .10 in the pregnant population the probability of concluding that the populations are different is small (less than 4%). If the true cumulative probability reaches .30 then the probability of finding a difference increases to .81, indicating that this difference would be missed 19% of the time. Finally, if the true cumulative probability reaches .40 then the probability of finding a difference is .97, indicating that this difference would be missed only 3% of the time.

Since Arm 3.2 includes women receiving either ATV/r or DRV/r, and approximately half of the women in this arm are anticipated to be on each combination, the above calculations were also done for a sample size of 12 women. With a sample size of 12 women (for ATV/r and DRV/r, respectively), adequate exposure will be defined as fewer than 4 out of 12 evaluable pregnant women having PK exposure parameters below the 10<sup>th</sup> percentile for the non-pregnant population. Given the discrete nature of the data, if 4 or more participants have low PK exposure parameters, the lowest sample probability that can be achieved is 33%, 4 out of 12, and the exact 80% confidence limits are (15%, 56%). These confidence limits exclude the tenth percentile and indicate that the protocol team is at least 90% confident that the true percentage of pregnant women having PK parameters below the 10<sup>th</sup> percentile for the non-pregnant population is greater than 10%. Table 8 provides the probability of finding the exposure of the pregnant population to be lower than that of the non-pregnant population given the current dose with a sample size of 12 evaluable women. If the true cumulative probability corresponds to .10 in the pregnant population, the probability of concluding that the populations are different is small (less than 3%). If the true cumulative probability reaches .30 then the probability of finding a difference increases to .51, indicating that this difference would be missed 49% of the time. Finally, if the true cumulative probability reaches .40 then the probability of finding a difference is .77, indicating that this difference would be missed 23% of the time. Note that the smaller sample size of 12 leads to a wider confidence interval and larger probability of missing a true difference (decreased power) compared with a sample size of 25.

**Table 8. Probabilities of concluding that the exposure of the pregnant population is lower than that of the non-pregnant population with sample sizes of 25 and 12 evaluable women**

True cumulative probability associated with the value for the 10 <sup>th</sup> percentile from the non-pregnant population in the pregnant population	Probability of concluding that the exposure of the pregnant population is lower than the non-pregnant population (N=25)	Probability of concluding that the exposure of the pregnant population is lower than the non-pregnant population (N=12)
.10	.033	.026
.20	.38	.21
.30	.81	.51
.40	.97	.77

For Components 1, 3, and 4, ARV and TB treatment drugs will also be studied in a repeated measures design, in which each woman will be measured during pregnancy and postpartum or in the second and third trimester, depending on the specific drug being studied (this analysis is called the Stage 2 analysis in [Section 9.6](#)). The comparisons will be made at the within participant level, using the Wilcoxon signed-rank test and 90% confidence limits for the geometric mean ratio of the PK exposure parameter in the two conditions (pregnant versus non-pregnant, or second versus third trimester). At this stage of the analysis, the test and confidence interval are assessing whether the drug exposure differs in the two conditions.

Based on past experience in P1026s, the standard deviation on the log scale for the within-participant ratio of the PK exposure parameter in the two conditions (during pregnancy and postpartum) has ranged from 0.3 to 1.1. [Table 9](#) illustrates the width of the confidence limits for the geometric mean ratio and whether they would exclude the value of 1.0 according to the standard deviation (SD) and observed point estimate, assuming that 12 or 25 participants have both antepartum and postpartum (or both second and third trimester) evaluable PK parameter measurements. If the CI exclude 1.0, this would indicate that the PK exposure parameter is significantly lower (or higher) in one condition than in the other, with one-sided p-value <0.05 (two-sided p-value <0.10). The dark shaded areas represent cases where the confidence limits exclude the value 1.0. For example, with 12 evaluable participants, if the geometric mean of the observed ratios is 1.0 and the SD of the natural log observed ratio is 0.3, then the 90% CI would be 0.86 to 1.17 so the true ratio of the geometric mean PK exposure parameter is likely to be close to one with high confidence. These results would indicate that no statistically significant difference between the pregnant and non-pregnant conditions was observed. For a SD of 0.3, with 12 or 25 evaluable participants, the ratio would need to be as large as 1.25 (or as small as 0.80 to indicate a detectable difference between the two conditions (that is for the confidence limits to exclude the value 1.0). If the SD is 0.5 or 0.7, with 12 evaluable participants, a ratio of 1.5 or greater (or 0.67 or smaller) would be required to indicate a detectable difference; however, with 25 evaluable participants, the confidence intervals are narrower, and power is correspondingly higher (with an SD of 0.5 and 25 evaluable participants, the ratio would only need to be 1.25 or greater, or 0.8 or smaller, to indicate a detectable difference). If the SD is 0.9 or higher, with 12 evaluable participants, a ratio of 2 or greater (or 0.5 or smaller) would be required to indicate a detectable difference, however with 25 evaluable participants, a ratio of 1.5 or greater (or 0.67 or smaller) would be required to indicate a detectable difference.

Note: The above examples are provided to give the reader a sense for the magnitude of the differences that will be detectable, based on the information in the following table. During the study, confidence limits will be calculated for the actual observed ratios and SD.

**Table 9. 90% Confidence Limits for the Geometric Mean Ratio of the PK Exposure Parameter (n=12 and n=25)**

<b>SD</b>	<b>OBS_RATIO</b>	<b>Lower Confidence Limit (LCL) [N=12]</b>	<b>Upper Confidence Limit (UCL) [N=12]</b>	<b>Lower Confidence Limit (LCL) [N=25]</b>	<b>Upper Confidence Limit (UCL) [N=25]</b>
0.3	0.25	0.21	0.29	0.23	0.28
	0.5	0.43	0.58	0.45	0.55
	0.67	0.57	0.78	0.60	0.74
	0.80	0.68	0.94	0.72	0.89
	1	0.86	1.17	0.90	1.11
	1.25	1.07	1.46	1.13	1.39
	1.5	1.28	1.75	1.35	1.66
	2	1.71	2.34	1.80	2.22
	4	3.42	4.68	3.61	4.43
0.5	0.25	0.19	0.32	0.21	0.30
	0.5	0.39	0.7	0.42	0.59
	0.67	0.52	0.87	0.56	0.79
	0.80	0.62	1.04	0.67	0.95
	1	0.77	1.30	0.84	1.19
	1.25	0.96	1.62	1.05	1.48
	1.5	1.16	1.94	1.26	1.78
	2	1.54	2.59	1.69	2.37
	4	3.09	5.18	3.37	4.75
0.7	0.25	0.17	0.36	0.20	0.32
	0.5	0.35	0.72	0.39	0.64
	0.67	0.47	0.96	0.53	0.85
	0.80	0.56	1.15	0.63	1.02
	1	0.70	1.44	0.79	1.27
	1.25	0.87	1.80	0.98	1.59
	1.5	1.04	2.16	1.18	1.91
	2	1.39	2.88	1.57	2.54
	4	2.78	5.75	3.15	5.08
0.9	0.25	0.16	0.40	0.18	0.34
	0.5	0.31	0.80	0.37	0.68
	0.67	0.42	1.07	0.49	0.91
	0.80	0.50	1.28	0.59	1.09
	1	0.63	1.60	0.73	1.36
	1.25	0.78	1.99	0.92	1.70
	1.5	0.94	2.39	1.10	2.04
	2	1.25	3.19	1.47	2.72
	4	2.51	6.38	2.94	5.44
1.1	0.25	0.14	0.44	0.17	0.36
	0.5	0.28	0.88	0.34	0.73
	0.67	0.38	1.18	0.46	0.98
	0.80	0.45	1.41	0.55	1.17
	1	0.57	1.77	0.69	1.46



SD	OBS_RATIO	Lower Confidence Limit (LCL) [N=12]	Upper Confidence Limit (UCL) [N=12]	Lower Confidence Limit (LCL) [N=25]	Upper Confidence Limit (UCL) [N=25]
	1.25	0.71	2.21	0.86	1.82
	1.5	0.85	2.65	1.03	2.18
	2	1.13	3.54	1.37	2.91
	4	2.26	7.07	2.75	5.83

Legend:

OBS\_RATIO is the anti-log of the mean of the log ratios of the PK exposure parameters for the pregnant versus non-pregnant conditions (or second vs. third trimester).

SD represents SD of the natural log of the observed ratio (OBS\_RATIO).

LCL and UCL are the lower and upper confidence limits, respectively, assuming a Student's t distribution with n=12 or N=25.

The dark-shaded rows represent cases where the CI excludes the value 1.0, indicating that the PK exposure differs significantly in the pregnant vs. non-pregnant conditions (or second vs. third trimester).

## 9.4.2 Accrual

Each arm will open to accrual independently and will accrue independently over approximately 36 months from the first enrollment in each arm.

It is difficult to project the exact accrual period and total number of enrollments needed to achieve the target number of evaluable participants in each arm, because the actual enrollment needed for each arm and total enrollment will depend on several factors:

- Participants who do not have evaluable data will be replaced, but will still be counted in the enrollment for that arm (which may therefore exceed the target number of evaluable);
- Enrollment to an arm may be restricted or adjusted upward (above the target number of evaluable but only to the maximum enrollment of that arm – see Table 7) so that evaluable second trimester PK data are obtained from at least 12 women;
- Enrollment to an arm may be adjusted upward to obtain additional evaluable infant washout or maternal second-line TB PK data
- An arm may be closed early due to slow accrual or if PK targets are not met in 6 women, at any time after at least 12 women have been enrolled.
- An arm may be closed early if the target number of evaluable participants is reached before the enrollment limit is reached.

Since the current protocol version has a total of 13 arms, 10 arms with an enrollment limit of 28 women per arm and 3 arms with an enrollment limit of 15 women, a maximum of 325 women may be enrolled, as well as their infants.

## 9.5 Monitoring

Implementation of this study will be monitored at multiple levels, consistent with standard IMPAACT procedures. Detailed plans for study monitoring will be outlined in a Study Progress, Data, and Safety Monitoring Plan (SPDSMP) developed by the Statistical and Data Management Center (SDMC) prior to enrollment of the first participant. [Sections 11](#) and [12](#) provide more information on on-site monitoring and quality management at the site level. Further information on monitoring of study progress, quality of study conduct, and participant safety across sites is provided below:

## 9.5.1 Monitoring by the Protocol Team

### ***Study Progress and Quality of Study Conduct***

The Protocol Team is responsible for continuous monitoring of study progress, including timely achievement of key milestones, and quality of study conduct.

The team will closely monitor total study accrual and arm-specific accrual based on reports that will be generated at least monthly by the SDMC. For TB drug arms carrying over from the P1026s study, accrual reports from both studies will be monitored together as data from both studies may be combined for analysis. Accrual performance will be reported by the DMC, by site and across sites, and the team will review and discuss study progress at least monthly.

The Protocol Team will similarly review participant retention and other key indicators of the quality of study conduct (e.g., data and specimen completeness) based on reports generated by the SDMC and take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation.

Determination of PK evaluability will be made by a protocol pharmacologist and tracked in the study database. If a participant is deemed unevaluable, the Core Protocol Team will determine how to proceed with replacement, and the SDMC will implement the decision in the data management system and SES.

### ***Participant Safety***

On behalf of the Protocol Team, the Core Protocol Team will closely monitor participant safety through routine review of safety data reports generated by the SDMC. These reports will provide listings of adverse events specified for entry into eCRFs, as described in [Section 7.2](#). The Core Protocol Team will review these reports via conference call or other meeting at least monthly. At the time of each call, the DAIDS Medical Officer may, when possible, also review any EAEs (defined in [Section 7.3](#)) reported to the DAIDS Safety Office that are not yet reflected in the data reports. As drugs are not being provided in this study, there are no planned safety-related study action triggers or stopping rules; however, the Core Protocol Team (and specifically, the clinician members) will continually evaluate the pattern and frequency of reported events and assess for any individual occurrences or trends of concern. If recurrent instances in an individual arm of a serious toxicity are observed, appropriate authorities, such as the FDA and/or the pharmaceutical company, may be notified.

### ***Interim PK Exposure Monitoring During Pregnancy (for selected ARV arms only)***

Based on data regarding the ARV drugs presently under study, the major concern is that the ARV drug exposure in pregnant women will be lower than that of the non-pregnant population, and the interim PK exposure monitoring rules are designed to detect this scenario quickly. For selected study arms (see [Section 10.4.2](#)), at any time after a minimum of 12 participants have been enrolled, if six or more pregnant women have the third-trimester PK exposure parameter below the 10<sup>th</sup> percentile for the non-pregnant population, the Core Protocol Team will evaluate the adequacy of drug exposure in that arm, and with the agreement of the Medical Officers, determine whether enrollment to that arm should continue. The exact 80% confidence limits for 6 participants with low drug exposure out of a total of 25 are (13%, 38%), which exclude 10% and

indicate strong evidence that the distribution of the PK parameter of interest for the pregnant women is different from that for the non-pregnant women (see Section 9.4 for details). If a statistical difference appears to be clinically important, then enrollment into that study arm will stop.

Since Arm 3.2 includes women receiving either ATV/r or DRV/r, and approximately half of the women in this arm are anticipated to be on each combination, the above monitoring rule needs to be modified for ATV and DRV in Arm 3.2 (but not RTV, because all Arm 3.2 women will receive RTV): if four or more pregnant women receiving ATV or four or more pregnant women receiving DRV have the third-trimester PK exposure parameter below the 10<sup>th</sup> percentile for the non-pregnant population, the Core Protocol Team will evaluate the adequacy of exposure to that drug (ATV or DRV), and with the agreement of the Medical Officers, determine whether enrollment of women on that drug should continue. The exact 80% confidence limits for 4 participants with low drug exposure out of a total of 12 are (15%, 56%), which exclude 10% and indicate strong evidence that the distribution of the PK parameter of interest for that drug in pregnant women is different from that for the non-pregnant women (see Section 9.4 for details).

### 9.5.2 Monitoring by the Study Monitoring Committee (SMC)

An independent IMPAACT SMC will review this study regularly, following policies described in the IMPAACT MOP.

SMC reviews will occur at least annually and on a more frequent or *ad hoc* basis if any issues or concerns arise or are raised by the Core Protocol Team (particularly with regard to participant safety). Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges that may be identified during their reviews.

The SMC will monitor study progress, quality of study conduct, and participant safety. The SMC will generally review the same types of data reports as the Protocol Team and Core Protocol Team. For *ad hoc* reviews, more limited data may be reviewed, focusing on the events that triggered the reviews.

## 9.6 Analyses

The data analyses to address the primary, secondary, and other pharmacokinetic objectives will include descriptive statistics for the PK parameter of interest at each study visit. Descriptive statistics will include the mean and median as measures of location and the standard deviation, interquartile range, and range as measures of dispersion. For certain arms (specified below), the data analyses to address the primary objectives will also include comparisons of the PK parameter of interest between two conditions (pregnant vs. non-pregnant, second vs. third trimester). Each analysis will include all participants with evaluable data for that analysis. A participant's data will be deemed unevaluable for a specific analysis if they do not have adequate pharmacokinetic evaluations to determine the pharmacokinetic exposure parameter of interest for that analysis (see 9.6.1 below for details). For the secondary objectives to describe safety and clinical outcomes, adverse events and other safety outcome measures will be tabulated, and descriptive statistics (mean, median, standard deviation, interquartile range, and range) will be calculated for plasma HIV-1 RNA measurements and CD4 cell counts. If the study arms enroll at different rates, the data analysis for an arm may be done when data collection for the primary outcome measure for that arm is complete.

Within-participant comparisons (e.g., between pregnant versus non-pregnant conditions, or second versus third trimester) will be performed for continuous outcome measures using the Wilcoxon signed-rank test and for dichotomous outcome measures using McNemar's test. Between-participant comparisons will be performed for continuous outcome measures using the Wilcoxon rank-sum test and for dichotomous outcome measures using the chi-square or Fisher exact test. 90% confidence limits for the geometric mean ratio of the PK exposure parameter in the pregnant versus non-pregnant conditions will also be calculated to describe the range of values that are consistent with the observed data and help the protocol team assess whether there is a clinically important difference in exposure in the two conditions. The confidence coefficient will be 90% rather than 95% to match the usual practice in the pharmacokinetic literature.

As noted in [Section 9.1](#), the comparisons to be performed to address the primary objectives for certain arms will vary according to type of drug and timing of sampling. [Table 10](#) summarizes these comparisons for each type of arm. The analyses for the Component 1 intracellular PK arms, Component 2 arms, and Component 5 arms are not listed in [Table 10](#) because these analyses will be purely descriptive and will not include any comparisons.

The analysis of ARV drug PK parameters during pregnancy will follow a two or three stage approach. In Stage 1, an individual woman's PK exposure parameter during pregnancy will be compared in real time to the 10<sup>th</sup> percentile for that PK exposure parameter for that drug from a non-pregnant population, and the woman and her clinical provider will be notified if the woman's value is below the 10<sup>th</sup> percentile. If there is strong evidence that the true percentage of pregnant women having the PK exposure parameter below the 10<sup>th</sup> percentile for the non-pregnant population is greater than 10%, the protocol team will evaluate whether to stop enrollment early and whether to recommend that additional study of the drug/drug combination is necessary (see Interim PK Exposure Monitoring During Pregnancy (for selected ARV arms only) in [Section 9.5.1](#)).

**Table 10. PK Parameter Comparisons to be Performed for Each Type of Drug for the Primary Objectives**

Type of Study Arm	Analysis Stage	Description of Pharmacokinetic Parameter Comparison	Type of Comparison
ARV without TB Drugs (Component 1, excluding TAF intracellular PK arms)	Stage 1	Antepartum plasma PK parameter vs. 10 <sup>th</sup> percentile from external, non-pregnant population	Between-participant
	Stage 2	Antepartum vs. postpartum plasma PK parameters	Within-participant
ARV with First-line TB treatment drugs (Component 3)	Stage 1	Antepartum ARV PK parameter vs. 10 <sup>th</sup> percentile from non-pregnant population	Between-participant
	Stage 2	Antepartum vs. postpartum ARV PK parameters	Within-participant
	Stage 3	ARV PK parameter with TB treatment drugs vs. ARV PK parameter without TB treatment drugs in previous P1026s or 2026 arm (if available)	Between-participant
First-line TB treatment drugs with ARVs* (Component 3)	Stage 2	Antepartum vs. postpartum TB drug PK parameter	Within-participant**
Second-line TB treatment drugs with or without ARVs* (Component 4)	Stage 2	Antepartum vs. postpartum TB drug PK parameters	Within-participant**
*Interim AUC monitoring (Stage 1 analysis) is not done for these arms (only done for ARVs during pregnancy).			
** This comparison may have a smaller sample size than 25 or may not be possible for certain TB treatment drugs because some women may complete their TB treatment before the postpartum PK visit and some TB treatment drugs are less commonly used than others (the total sample size per arm is 25 evaluable women on all TB drugs combined, not per TB drug).			

Stage 2 for the ARV drugs taken during pregnancy will implement a repeated measures design, in which antepartum and postpartum measurements from each woman will be compared at the within participant level, using the Wilcoxon signed-rank test to assess whether there is a statistically significant difference in the PK exposure parameter in the pregnant versus non-pregnant conditions. 90% confidence limits for the geometric mean ratio of the PK exposure parameter in the pregnant versus non-pregnant conditions will also be calculated to describe the range of values that are consistent with the observed data and help the protocol team assess whether there is a clinically important difference in exposure in the pregnant versus non-pregnant conditions.

For the ARV drugs being taken with first-line TB treatment drugs, in addition to Stages 1 and 2, a third stage of analysis (Stage 3) may be performed to compare the ARV PK exposure with first-line TB treatment drugs to the PK exposure for these ARVs without first-line TB treatment drugs, if studied in previous arms of IMPAACT P1026s or 2026. This analysis will involve a between-

participants comparison of PK exposure parameters at the same time point (e.g., second trimester, third trimester, postpartum) using the two-sample Wilcoxon rank sum test. The 90% confidence limits for the geometric mean ratio of the PK exposure parameters in the two groups of women at the same time point will also be calculated.

For the first-line TB treatment drugs, the PK analysis will use the Stage 2 approach described above, in which a within-participants comparison of TB drug PK exposure during pregnancy and postpartum will be performed, separately for HIV-infected and HIV-uninfected women in each study arm. Note that the sample size for this comparison may be less than the desired 25 evaluable women per drug because the total sample size per arm is 25 evaluable women on all TB drugs combined, not per TB drug, and because some women may complete their TB drug course before the postpartum visit where the PK sampling will be done.

For the second-line TB treatment drugs, the PK analysis will use the Stage 2 approach described above, in which a within-participants comparison of TB drug PK exposure during pregnancy and postpartum will be performed. Note that the sample size for these comparisons may be less than the desired 25 evaluable women per drug because the total sample size per arm is 25 evaluable women on all TB drugs combined, not per TB drug, and because some women may complete their TB drug course before the postpartum visit where the PK sampling will be done. It may or may not be possible to perform a Stage 3 between-participants comparison of second-line TB drug PK exposure in HIV-infected versus HIV-uninfected women at the same time point; depending on the number of women receiving each TB drug, it may be necessary to combine data from HIV-infected and HIV-uninfected women.

Further details of the analyses will be included in a separate Statistical Analysis Plan.

### **9.6.1 Unevaluable Participants**

For the Stage 1 analysis, Stage 3 analysis, and for calculation of descriptive statistics for a PK parameter at a specific time point for women or infants, a participant's data will be deemed unevaluable if they do not include adequate pharmacokinetic evaluations to determine the PK parameter of interest. For intracellular PK evaluations, one consideration for determining evaluability is whether the participant was at steady state based on the ARV start date.

For the Stage 2 analysis, a woman's data will be deemed unevaluable if (a) they do not include adequate pharmacokinetic evaluations to determine the PK parameters of interest under both the pregnant and non-pregnant conditions (or both second and third trimester), or (b) the participant's dosing regimen changed between the pregnant and non-pregnant conditions (or between the second and third trimester evaluation) in a way that was not specified in the protocol, or (c) there is a change in the underlying treatment during that time period (e.g., no longer receiving the drug under study, or receiving a disallowed medication). Changes in underlying treatment as well as data completeness will be monitored in order to replace unevaluable participants in a timely fashion.

For the purposes of determining protocol enrollment, definitions of evaluable participants for each component can be found in [Sections 3.1—3.5](#).

## 10 CLINICAL PHARMACOLOGY PLAN

### 10.1 Pharmacology Overview and Objectives

The overarching pharmacology goal is to assess, if possible, whether the level of exposure to the drugs under study during pregnancy, postpartum, and lactation is adequate or inadequate, based upon current knowledge. The study will aim to describe the PK of ARV and TB treatment drugs, provided as part of clinical care or through a research study, during pregnancy and postpartum. This study will also determine the washout PK of transplacentally-acquired ARV and TB treatment drugs in infants born to mothers receiving ARV drugs during pregnancy, as well as the breast milk transfer of these drugs from lactating mothers to breastfeeding infants.

The study is comprised of 5 components: (1) Pregnant WLHIV receiving oral ARVs and no TB drugs, and their infants (2) WLHIV and HIV-uninfected women who have received long-acting/extended release ARVs during pregnancy, and their infants (3) Pregnant WLHIV receiving ARVs and first-line TB treatment, and their infants (4) pregnant WLHIV and HIV-uninfected women receiving second-line TB treatment, and their infants (5) Postpartum WLHIV breastfeeding while receiving oral ARV, and their infants. The study design for each component is detailed in Section 3.

The pharmacology objectives of this study include all objectives listed in [Section 2](#), except for objectives 2.2.1 and 2.3.2.

### 10.2 Pharmacology Outcome Measures

*Note: The numbering of the outcome measures in this section corresponds to the numbering of the objectives in [Section 2](#).*

The PK outcome measures are shown below in [Table 11](#). The target PK parameters for each arm are specified in [Appendix V](#).

**Table 11. PK Outcome Measures**

<b>Primary PK Outcome Measures</b>	
10.2.1.1	<ul style="list-style-type: none"> <li>• Arms 1.1, 1.2: BIC, DOR:               <ul style="list-style-type: none"> <li>○ # of women who met AUC target in second trimester (2T), third trimester (3T) and postpartum (PP);</li> <li>○ AUC in 2T, 3T and PP</li> </ul> </li> <li>• Arms 1.3, 1.4, 1.5: TFV-DP concentrations in PBMCs and DBS in 2T, 3T and PP</li> </ul>
10.2.1.2	<ul style="list-style-type: none"> <li>• Arm 2.1: CAB:               <ul style="list-style-type: none"> <li>○ Cord blood/maternal plasma concentration ratio at delivery</li> <li>○ Infant washout half-life after delivery (if not breastfeeding)</li> <li>○ Maternal breast milk/maternal plasma concentration ratio (if breast feeding)</li> <li>○ Infant plasma concentration at breast milk PK visit (if breast feeding)</li> </ul> </li> </ul>
10.2.1.3	<ul style="list-style-type: none"> <li>• Arms 3.1, 3.2 and 3.3: DTG, ATV, DRV, LPV, INH, RIF, RFB, EMB, PZA, MFX: AUC at 2T, 3T and PP</li> </ul>
10.2.1.4	<ul style="list-style-type: none"> <li>• Arm: 4.1 MFX, LFX, CFZ, LZD, BDQ, DLM: AUC at 2T, 3T, and PP</li> </ul>
10.2.1.5	<ul style="list-style-type: none"> <li>• Arms 5.1, 5.2, 5.3:               <ul style="list-style-type: none"> <li>○ Maternal breast milk/maternal plasma concentration ratio</li> <li>○ Infant plasma concentration</li> </ul> </li> </ul>
<b>Secondary PK Outcome Measures</b>	
10.2.2.2	<ul style="list-style-type: none"> <li>• Components 1, 3 and 4, all Arms: Ratio of cord blood concentration to maternal blood concentration</li> </ul>
10.2.2.3	<ul style="list-style-type: none"> <li>• Components 1, 3 and 4, all Arms: Infant washout half-life of drug after birth (if the infant is not breastfeeding, and if the half-life is estimable)</li> </ul>
10.2.2.4	<ul style="list-style-type: none"> <li>• Components 3 and 4, if assessed:               <ul style="list-style-type: none"> <li>○ Maternal breast milk/maternal plasma concentration ratio</li> <li>○ Infant plasma concentration</li> </ul> </li> </ul>
10.2.2.5	<ul style="list-style-type: none"> <li>• Component 4 efavirenz, lopinavir, atazanavir, darunavir, dolutegravir, and/or raltegravir: AUC at 2T, 3T, and PP</li> </ul>
<b>Other PK Outcome Measures</b>	
10.2.3.1	<ul style="list-style-type: none"> <li>• Components 1-4, if assessed: Free fraction of ARV or TB drug at 2T, 3T and PP</li> </ul>

### 10.3 Pharmacology Data

PK sampling data to be source documented and entered into eCRFs for each drug under study being sampled at each PK sampling visit, by type of PK sampling, are described below in [Table 12](#). All PK data to be accessioned are described in more detail in the Pharmacology Data Monitoring Plan.



**Table 12. Documentation Requirements for PK Sampling Data**

<b>PK Sampling Visit Type</b>	<b>Source Document and Enter into eCRFs</b>
Intensive/Sparse PK	<ul style="list-style-type: none"> <li>• Date, time and amount of last two doses of the drug under study prior to observed dose on day of PK sampling, and of observed dose on day of PK sampling</li> <li>• Last two maternal meals and food intake around the observed dose(s), to include dates, times and descriptions</li> <li>• Date and time PK samples drawn</li> <li>• Date, time and amount of last doses of all other medications taken in last 7 days</li> </ul>
Breast Milk Transfer PK	<ul style="list-style-type: none"> <li>• Date, time and amount of last three doses of ARV or TB drug(s) under study prior to PK sampling visit</li> <li>• Last two maternal meals and food intake around the most recent dose(s) before the breast milk sample, to include dates, times and descriptions</li> <li>• Date and time PK samples drawn</li> <li>• Infant feeding history</li> </ul>
Cord Blood and Maternal Delivery	<ul style="list-style-type: none"> <li>• Date, time and amount of last doses of all drugs under study before delivery</li> <li>• Date and time of maternal blood drawing</li> <li>• Date and time cord blood obtained</li> </ul>
Infant Washout PK	<ul style="list-style-type: none"> <li>• Date and time PK samples drawn</li> </ul>

## 10.4 PK Data Analysis and Reporting of Results

All methods will be standardized with a filed Methods Report. Results from U.S.-based laboratories to be used in clinical care will be performed under CLIA conditions. Standard PK analyses using model dependent and independent PK approaches will be used to analyze drug concentration data. Refer to [Section 6.10](#) for maternal and infant PK sampling procedures.

Maternal plasma samples to be assayed for select ARV drugs (Arms 1.1, 1.2, 3.1, 3.2, 3.3, and 4.1) will be shipped to designated PK testing laboratories in real-time. Maternal DBS and PBMC samples for intracellular TAF assays (Arms 1.3, 1.4, and 1.5) will be stored on-site and then shipped for batch testing according to the schedule listed in the LPC. Summary statistics of intracellular concentrations will be generated. Population analysis may also be performed. Maternal plasma, PBMC, DBS, and breast milk samples to be assayed for ARV drugs (except those that will be tested real-time as specified above), and/or TB treatment drugs— as well as infant samples for washout and breast milk transfer assays — will similarly will be stored on-site and then shipped for batch testing, according to the schedule listed in the LPC. Any residual or remnant samples remaining after protocol-specified assays are performed will be destroyed.

### 10.4.1 PK Parameters

The typical PK parameters to be calculated for each PK sample type are as follows:

- Maternal intensive sampling schedule: Pre-dose concentration,  $C_{\tau}$  (end of sampling interval),  $T_{\min}$ ,  $C_{\min}$ ,  $T_{\max}$ ,  $C_{\max}$ , AUC, CI/F, V/F,  $t_{1/2}$ .
- Maternal sparse sampling schedule: intracellular ARV concentrations in PBMCs and DBS
- Infant washout sampling:  $t_{1/2}$ , drug concentrations

- Maternal/Infant breast milk transfer sampling: maternal breast milk/plasma concentration ratio, estimated absolute and relative cumulative infant doses, plasma concentrations in the breastfed infant

## 10.4.2 Reporting of PK Results to Sites

For select ARVs during pregnancy (Arms 1.1, 1.2, 3.1, 3.2, 3.3 and 4.1), results of individual plasma concentration assays will be reported to site investigators for pregnant women (antepartum samples) only, with results usually provided to sites within three weeks of sample receipt at the PK testing laboratory, unless the evaluations require further investigation or queries. In these circumstances, results will be provided as soon as the issue(s) has been resolved. PK reports will include estimated AUC or trough values and a comparison with concentration-time profiles derived from non-pregnant adult values. For cases in which the PK parameter of interest (AUC or trough) is below the 10<sup>th</sup> percentile of non-pregnant adult values, the reports will also include a notice to the site investigator that the value observed for the participant may be sub-therapeutic and that advice may be requested from the protocol pharmacologist regarding possible dosing adjustment. Any such request regarding advice on dosing adjustments should be emailed to the Core Protocol Team. 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 per [Section 6.6](#). 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.

No other individual results will be reported to site investigators. The protocol team routinely reviews results from interim PK analyses for presentations at meetings or final PK analyses for publication.

## 11 DATA HANDLING AND RECORD KEEPING

### 11.1 Data Management Responsibilities

As described in [Section 4.7](#), data on enrollment in this study will be collected using the DMC SES. Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled women and mother-infant pairs, including paper-based CRFs (if used), eCRFs, and supporting source data. In maintaining these records, sites must comply with the standards of source documentation specified in the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available on the website referenced in [Section 11.2](#)).

eCRFs and an eCRF completion guide will be made available to study sites by the DMC. Study site staff will enter required data into eCRFs, with system checks applied and data queries generated immediately upon saving the entered data. Data must be entered within timeframes specified by the DMC; queries must also be resolved in a timely manner. Selected laboratory data will be transferred electronically to the DMC through the LDMS.

Further information on eCRFs and IMPAACT data management procedures will be provided by the DMC. A User Manual for the Subject Enrollment System is available on the DMC portal at: <https://www.frontierscience.org>.

## 11.2 Essential and Source Documents and Access to Source Data

All DAIDS policies referenced in this section are available at:  
<https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures>

Study sites must comply with DAIDS policies on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. In its policy on Requirements for Manual of Operational Procedures, DAIDS requires sites to establish SOPs for maintaining essential and source documents in compliance with these policies. Site SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study, and site SOPs should be followed throughout the study.

Per the DAIDS policy on Storage and Retention of Clinical Research Records, study records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility during the conduct of the study and after the study is completed. Records must be retained for a minimum of three years after the completion of the study. Per 21 CFR 312.62, records must be maintained for two years after the date a marketing application is approved for one or more of the drugs under study for the indication for which it is evaluated in this study; or, if no application is filed, or if the application is not approved for this indication, records must be retained two years after the study is discontinued and the FDA is notified.

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, IMPAACT, the US Food and Drug Administration, site drug regulatory authorities, site IRBs/ECs, Office for Human Research Protections (OHRP), and other US, local, and international regulatory entities. Records must be kept on-site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID or NICHD. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID or NICHD.

## 11.3 Quality Control and Quality Assurance

Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the DAIDS policy on Requirements for Clinical Quality Management Plans, which is available at:  
<https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures>

## 12 CLINICAL SITE MONITORING

Site monitors under contract to NIAID or NICHD will visit study sites to inspect study facilities and review participant study records — including informed consent forms, paper-based CRFs (if used), eCRFs, medical records, laboratory records, and pharmacy records — to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records.

The monitors also will review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by the monitors.

## **13 HUMAN SUBJECTS PROTECTIONS**

### **13.1 Institutional Review Board/Ethics Committee Review and Approval**

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific informed consent and assent forms in accordance with 45 CFR 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must also promptly report to the IRBs/ECs any changes in the study and any unanticipated problems involving risks to participants or others.

All IRB/EC policies and procedures must be followed and complete documentation of all correspondence to and from the IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Manual (see also [Section 14.2](#)).

### **13.2 Vulnerable Participants**

The NIH is mandated by law to ensure that pregnant women and children be included in clinical research when appropriate (126, 127). This study responds to that mandate and will provide clinical research data to inform ARV and TB treatment guidelines for pregnant women. Nonetheless, the pregnant women, fetuses, and children who take part in this study are considered vulnerable participants per the US Code of Federal Regulations (CFR), and site IRBs/ECs must consider the potential risks and benefits to maternal, fetal, and infant participants as described in 45 CFR 46 Subpart B (for pregnant women, fetuses, and neonates) and 45 CFR 46 Subpart D (for children).

With respect to 45 CFR 46 Subpart B, the specifications of 45 CFR 46.204 (d) are considered to apply to Components 1, 2, 3, and 4; therefore, maternal participants of those components will be asked to provide written informed consent or assent for their own and their children's study participation.

With respect to 45 CFR 46 Subpart D, the specifications of 45 CFR 46.404 are generally expected to apply to maternal participants not of legal age to consent in Component 2, and to infants in Components 2 and 5.

However, IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process described in [Section 14.2](#), and the risk category assigned by the IRB/EC further determines the parental informed consent requirements for the study at each site. Per 45 CFR 46.408 (b), the IRB/EC may find that the consent of one parent is sufficient for research to be conducted under 46.404 or 46.405. If the IRB/EC finds that the research is covered by 46.406 or 46.407, both parents must give their consent, unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child (as determined locally). IRBs/ECs must

document their risk determination, and study sites should adapt the signature pages of their site-specific ICFs as needed to accommodate the parental consent requirements associated with the IRB/EC determination.

Study sites must comply with the requirements of the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research, which is available at: <https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures>  
In addition to the US regulations cited above, sites not in the U.S. must also comply with all applicable local and national guidelines and regulations.

### 13.3 Informed Consent

Refer to [Section 4.7](#) and the study-specific MOP for further information on informed consent procedures for this study.

Sample component-specific independent informed consent forms are provided in [Appendix VI-A](#) through [Appendix VI-E](#) (see [Table 3](#) for summary) for maternal participants of legal age or otherwise able to provide independent informed consent for their own participation in the study. Per [Section 4](#), maternal participants not of legal age or otherwise able to provide independent informed consent may be included in this study in Component 2 only; the inclusion of these participants must be in accordance with local IRB/EC guidelines. Sample parent/guardian consent forms for Component 2 are included in [Appendix VII](#) and sample assent forms for Component 2 are included in [Appendix VIII](#). Sites enrolling participants not of legal age or otherwise able to provide independent informed consent must document all applicable laws, regulations, and IRB/EC policies and requirements pertaining to inclusion of youth in the research, and must establish SOPs for ensuring that these laws, regulations, and policies are upheld, particularly with regard to enrolling fetuses or infants of underage maternal participants.

Site investigators and their designees will be required to determine participant age and ability to provide independent informed consent for study participation consistent with IRB/EC policies and procedures. Each site must establish SOPs, roles, and responsibilities for completing these determinations, and study staff involved in completing these determinations must have documented training in the relevant policies and procedures prior to study initiation.

Written informed consent and written assent will be obtained for study participation as follows:

- *If the potential maternal participant is of legal age or otherwise able to provide independent informed consent as determined by site SOPs and consistent with site IRB/EC policies and procedures:* The potential participant must provide written informed consent for study participation for herself and her infant.

- *(Component 2 only): If the potential maternal participant is not of legal age or otherwise unable to provide independent informed consent as determined by site SOPs and consistent with site IRB/EC policies and procedures:* Parent/guardian or other legally authorized representative of the mother and her infant must provide written informed consent for the mother and her infant's study participation; in addition, the mother must also provide written assent for her and her infant's study participation. Written informed assent from the potential participant will be conducted per site IRB/EC policies and will generally be obtained if the participant is able to understand the nature, significance, and risks of the study. Note: Refer to [Section 13.2](#) for considerations related to parental consenting requirements; IRB/EC risk determinations will guide whether the consent of one or both parents may be required for this study. All IRB/EC requirements must be followed.

Written informed consent or assent (where applicable) for maternal and infant study participation will be obtained before any study-specific procedures are performed. The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. Participants will be extensively counseled on the importance of adherence to their prescribed ARV and/or TB regimen(s).

Where applicable, assent will be obtained through a similar process, with the amount of information and level of detail provided tailored to the age of the potential participant and guided by IRB/EC policies and procedures. For Component 2, it is anticipated that maternal participants not of legal age to provide independent consent will be adolescents. As such, each potential maternal participant who is not of legal age to provide independent informed consent is generally expected to take part in the informed consent process with her parent or legal guardian and both the assent of the participant and the consent of the parent or legal guardian will be required. For example, if the participant does not provide assent, or the parent or legal guardian does not provide consent, the participant will not be enrolled in the study.

For maternal participants who are not of legal age to provide independent consent at study entry, written informed consent must later be obtained if the legal age of consent is reached any time following entry. At the next scheduled visit after the legal age is reached, an informed consent process must be conducted with the participant. If written informed consent is obtained, the participant will continue in the study as originally planned; if written informed consent is not obtained, the participant will be discontinued from the study.

As indicated above, it is generally expected that mothers will provide informed consent for their own and their infant's participation in this study. However, parental consenting requirements at each site will depend on the IRB/EC risk determination described in [Section 13.2](#); all IRB/EC requirements will be followed.

As part of the informed consent or assent process, potential participants will be asked to explicitly document whether they agree to protocol-specified genetic testing. Protocol-specified genetic testing may be declined with no impact on other aspects of maternal or infant study participation.

Should the consenting parent or legal guardian of an enrolled underage maternal participant or an enrolled infant die or no longer be available for any reason, no further study-specific visits or procedures may be performed until informed consent for continued study participation is obtained from a locally authorized guardian. In accordance with the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research (available at the website referenced in [Section 13.2](#)), all study 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.

#### **13.4 Potential Benefits**

There may be no direct benefit to mothers and infants who take part in this study. However, mothers and infants may benefit from having more medical visits where they can be checked for safety of their medications. In some arms, mothers may also benefit from having the ARV levels in their blood measured. Information learned from this study may be of benefit to participants and others in the future.

#### **13.5 Potential Risks**

The potential risks of participation in this study include risks associated with study procedures. Most study procedures are routine medical procedures that are associated with minimal to no risk in participants. Blood collection may cause pain, bruising, swelling, or fainting. There is a very small chance of infection where the needle is inserted. It may be uncomfortable to express breast milk. Blood collection from infants will be done by heel stick, which may cause some discomfort, bleeding or bruising at the site of the heel stick.

#### **13.6 Reimbursement/Compensation Plan**

Pending IRB/EC approval, participants will be compensated for costs associated with completing study visits (e.g., transport costs). Participants at US sites will be compensated per visit based on local cost of living in amounts between \$20-\$300 per visit. The per visit compensation amounts will vary based on site location, and the number, duration and type of study visits that are completed and in some cases the number of specimens collected. Participants at non-US sites will be reimbursed at a rate to be determined based on local norms and in consultation with the local IRB/EC. Compensation amounts will be specified in site-specific ICFs and/or other materials as applicable per IRB/EC policies and procedures.

#### **13.7 Privacy and Confidentiality**

All study procedures will be conducted in private and every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing as described in [Section 11.2](#). Data or information from the study may be shared with drug companies who have agreements with IMPAACT and/or the U.S. NIH, or regulatory entities, but individual participants will not be identified.

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site (e.g., EAE report forms, photographs of observed reactions) will be identified by PID only. Likewise, communications between study staff and Protocol Team members regarding individual participants will identify participants by PID only.

Study sites are encouraged but not required by DAIDS policies to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

In addition to the above, a Certificate of Confidentiality has been obtained for this study from the US Department of Health and Human Services. This certificate protects study staff from being compelled to disclose study-related information by any US Federal, state, or local civil, criminal, administrative, legislative, or other proceedings. It thus serves to protect the identity and privacy of study participants. Because the certificate cannot be enforced outside of the US, however, it applies only to US sites and participants.

### **13.8 Communicable Disease Reporting**

Study staff will comply with local requirements to report communicable diseases, including HIV infection, identified among study participants to health authorities. Participants will be made aware of all applicable reporting requirements as part of the study informed consent process.

### **13.9 Management of Incidental Findings**

Site investigators will inform mothers (or other authorized guardians if applicable) of all clinically meaningful physical exam findings and laboratory test results, including results of HIV tests and hematology and chemistry tests, and certain PK test results (see [Section 10.4.2](#)). Site investigators will provide all clinically meaningful results of IMPAACT 2026 evaluations to the participant's clinical care providers or investigators from another research study who are responsible for drug management, for further follow-up. Site investigators may assist in referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

### **13.10 Management of New Information Pertinent to Study Participation**

Participating women will be provided with any new information learned over the course of the study that may affect their willingness to continue receiving the drug under study and/or remain in follow-up in the study.



## 14 ADMINISTRATIVE PROCEDURES

### 14.1 Regulatory Oversight

This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), which are part of the United States National Institutes of Health (NIH). Gilead Sciences, Inc., ViiV Healthcare, and Merck Research Laboratories will provide funding to support limited aspects of this study but will not provide regulatory sponsorship or oversight of the study.

Within the NIAID, DAIDS is responsible for regulatory oversight of this study. DAIDS will distribute safety-related information pertaining to the drugs under study prior to and during the conduct of the study, in accordance with its sponsor obligations.

NIAID and NICHD provide funding to the clinical research sites at which this study will be conducted. Each institute contracts with independent clinical site monitors who will perform monitoring visits as described in [Section 12](#). As part of these visits, monitors will inspect study-related documentation to ensure compliance with all applicable US and local regulatory requirements.

### 14.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol ICFs approved, as appropriate, by their local IRBs/ECs and any other applicable regulatory entity. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received.

Site-specific ICFs will be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

For any future protocol amendments, upon receiving final IRB/EC and any other applicable regulatory entity approvals, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received. Site-specific ICFs will not be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which is available on the RSC website:

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

### **14.3 Study Implementation**

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable US and local regulations. Study implementation will also be guided by the IMPAACT MOP, study-specific MOP, LPC, and other study implementation materials, which will be available on the study-specific website:

<https://impaactnetwork.org/studies/IMPAACT2026.asp>

Study implementation at each site will also be guided site-specific SOPs. The DAIDS policy on Requirements for Manual of Operations specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials (available on the website referenced in [Section 11.2](#)). These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

### **14.4 Protocol Deviation Reporting**

Per the policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available at the website referenced in [Section 11.2](#)), all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to site IRBs/ECs and other applicable review bodies in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported within IMPAACT, following procedures specified in the IMPAACT MOP.

### **14.5 Critical Event Reporting**

Per the DAIDS policy on Identification and Classification of Critical Events, a critical event is defined as an unanticipated study-related incident that is likely to cause harm or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity. All such events must be reported following procedures specified in the DAIDS Critical Events Manual, which is available at:

<https://www.niaid.nih.gov/sites/default/files/criticaleventsmanual.pdf>

### **14.6 ClinicalTrials.gov**

This protocol is subject to the United States Food and Drug Administration Amendments Act of 2007 (FDAAA), including registration in ClinicalTrials.gov.

## **15 PUBLICATIONS**

All presentations and publications of data collected in this study are governed by IMPAACT policies, which are available in the IMPAACT MOP.

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## APPENDICES

### Appendix I-A

#### Maternal Schedule of Evaluations for Component 1: Pregnant WLHIV on Oral ARVs and no TB Drugs

MATERNAL EVALUATIONS: COMPONENT 1	Screening	2 <sup>nd</sup> Trimester / Entry <sup>1</sup>	3 <sup>rd</sup> Trimester / Entry <sup>1</sup>	Delivery <sup>2</sup>	6-12 Weeks
<i>Visit Window</i>	-60 days	20 0/7-26 6/7 weeks of pregnancy	30 0/7-37 6/7 weeks of pregnancy	+/- 4 days	42 – 90 days
Informed Consent	X				
<b>CLINICAL EVALUATIONS</b>					
Medical and Medications History	X	X	X	X	X
Abbreviated Physical Exam		X	X	X	X
<b>LABORATORY EVALUATIONS</b>					
Confirmatory HIV testing [if needed]	[0-6 mL]				
Chemistries		5 mL	5 mL	5 mL	5 mL
Hematology		1 mL	1 mL	1 mL	1 mL
<b>IMMUNOLOGY</b>					
CD4 cell count		1 mL	[1 mL] <sup>3</sup>		
<b>VIROLOGY</b>					
HIV RNA		6 mL	6 mL	6 mL	6 mL
<b>PHARMACOLOGY EVALUATIONS FOR ARMS 1.1 AND 1.2</b>					
Intensive PK sampling <sup>4</sup>		17-19 mL <sup>8</sup>	17-19 mL <sup>8</sup>		17-19 mL
Alpha-1 acid glycoprotein <sup>5</sup>		X	X		X
Single PK sample				5 mL <sup>6</sup>	
Cord blood PK sample <sup>6</sup>				X	
DBS storage for pharmacogenetics <sup>7</sup>		X	[X]		
<b>PHARMACOLOGY EVALUATIONS FOR ARMS 1.3, 1.4 AND 1.5</b>					
Sparse PK sampling <sup>4</sup> (store plasma, DBS, and PBMC)		29 mL <sup>8</sup>	29 mL <sup>8</sup>		29 mL
Alpha-1 acid glycoprotein <sup>5</sup>		X	X		X
Single PK sample (also store DBS and PBMC)				11 mL <sup>6</sup>	
Cord blood PK sample <sup>6</sup> (also store DBS and PBMC)				X	
DBS storage for pharmacogenetics <sup>7</sup>		X	[X]		
<b>TOTAL MAXIMUM BLOOD VOLUME</b>	<b>6 mL</b>	<b>61 mL</b>	<b>61 mL</b>	<b>28 mL</b>	<b>61 mL</b>

[ ] indicate procedures that are not required for ALL participants at the specified visit.

#### APPENDIX I-A FOOTNOTES

- Entry may occur at the Second or Third Trimester visit. Women entering study at the Second Trimester visit will also complete the Third Trimester visit.
- Day of delivery is defined as Day 0 and all post-delivery follow-up visits are counted from this date.
- For women entering the study during the third trimester only.

4. See [Section 6.10.1](#).
5. Measured at the pharmacology laboratory from PK pre-dose sample for highly-bound ARVs only.
6. See [Section 6.10.2](#).
7. For women who have consented to genetic testing only, collect once, at second or third trimester, see [Section 6.11](#).
8. Initial PK sampling should be targeted to be performed within 5 days of enrollment but must be performed no later than 14 days after enrollment.

## Appendix I-B

### Maternal Schedule of Evaluations for Component 2: Pregnant WLHIV and HIV-uninfected women who Received Long-acting/Extended-release ARVs During Pregnancy

MATERNAL EVALUATIONS: COMPONENT 2	Screening / Entry	Delivery <sup>2</sup>	Post-Delivery <sup>1</sup>		
			5-9 Days <sup>3</sup> <i>(Breast milk transfer PK women only)</i>	12-16 Days <sup>3</sup> <i>(Breast milk transfer PK women only)</i>	3-5 Weeks <sup>3</sup> <i>(Breast milk transfer PK women only)</i>
<i>Visit Window</i>	24 0/7 weeks of pregnancy through day of delivery <sup>1</sup>	+/- 4 days	5-9 days	12-16 days	21-41 days
Informed Consent	X				
<b>CLINICAL</b>					
Medical History/Concomitant Medicines	X	X	X	X	X
Abbreviated Physical Exam	X	X	X	X	X
<b>LABORATORY</b>					
Chemistries		5 mL			
Hematology		1 mL			
<b>PHARMACOLOGY</b>					
Single PK sample		5 mL <sup>4</sup>	2 mL <sup>5</sup>	2 mL <sup>5</sup>	2 mL <sup>5</sup>
Alpha-1 acid glycoprotein <sup>6</sup>		X			
Cord blood PK sample		X <sup>3</sup>			
Breast milk sample <sup>5</sup>			5 mL	5 mL	5 mL
DBS storage for pharmacogenetics <sup>7</sup>		[X]			
<b>TOTAL MAXIMUM BLOOD VOLUME</b>	<b>0 mL</b>	<b>11 mL</b>	<b>2 mL</b>	<b>2 mL</b>	<b>2 mL</b>

[ ] indicate procedures that are not required for ALL participants at the specified visit.

#### APPENDIX I-B FOOTNOTES

1. Enrollment must occur prior to delivery.
2. Day of delivery is defined as Day 0 and all post-delivery follow-up visits are counted from this date
3. Only women who meet the requirements for breast milk transfer PK sampling will complete the 5-9 Days, 12-16 Days, and 3-5 Weeks visits, see [Section 6.10.4](#)
4. See [Section 6.10.2](#).
5. See [Section 6.10.4](#).
6. Measured at pharmacology laboratory from PK sample.
7. For women who have consented to genetic testing only, see [Section 6.11](#)

**Appendix I-C**  
**Maternal Schedule of Evaluations for Component 3: Pregnant WLHIV receiving ARVs and First-line TB Treatment**

MATERNAL EVALUATIONS: COMPONENT 3	Screening	2 <sup>nd</sup> Trimester / Entry <sup>1</sup>	3 <sup>rd</sup> Trimester / Entry <sup>1</sup>	Delivery <sup>2</sup>	Post-Delivery <sup>2</sup>		
					5-9 Days (Breast milk transfer PK women only) <sup>3</sup>	2- 8 Weeks	16 – 24 Weeks (Breast milk Transfer PK women only) <sup>3</sup>
Visit Window	-60 days	20 0/7-26 6/7 weeks of pregnancy	30 0/7-37 6/7 weeks of pregnancy	+/- 4 days	5-9 days	14-62 days	112-174 days
Informed Consent	X						
<b>CLINICAL</b>							
Medical and Medication History	X	X	X	X	X	X	X
Abbreviated Physical Exam		X	X	X	X	X	X
<b>LABORATORY</b>							
Confirmatory HIV testing [if needed]	[0-6 mL]						
Chemistries		5 mL	5 mL	5 mL		5 mL	
Hematology		1 mL	1 mL	1 mL		1 mL	
<b>IMMUNOLOGY</b>							
CD4 cell count		1 mL	[1 mL] <sup>4</sup>				
<b>VIROLOGY</b>							
HIV RNA		6 mL	6 mL	6 mL		6 mL	
<b>PHARMACOLOGY</b>							
Intensive PK sampling (ARV) <sup>5</sup>		14-16 mL <sup>11</sup>	14-16 mL <sup>11</sup>			14-16 mL	
Intensive PK sampling (TB) <sup>5</sup>		17-19 mL <sup>11</sup>	17-19 mL <sup>11</sup>			17-19 mL	
Alpha-1 acid glycoprotein <sup>6</sup>		X	X			X	
Single PK sample				5 mL <sup>7</sup>	4 mL <sup>8</sup>		4 mL <sup>8</sup>
Cord blood PK sample <sup>7</sup>				X			
Breast milk sample <sup>8</sup>					10 mL	[10 mL] <sup>9</sup>	10 mL
DBS storage for pharmacogenetics <sup>10</sup>		X	[X] <sup>4</sup>				
<b>TOTAL MAXIMUM BLOOD VOLUME</b>	<b>6 mL</b>	<b>48 mL</b>	<b>48 mL</b>	<b>17 mL</b>	<b>4 mL</b>	<b>47 mL</b>	<b>4 mL</b>

[ ] indicate procedures that are not required for ALL participants at the specified visit.

**APPENDIX I-C FOOTNOTES**

1. Entry may occur at the Second or Third Trimester visit. Women entering the study at the Second Trimester visit will also complete the Third Trimester visit.
2. Day of delivery is defined as Day 0 and all post-delivery follow-up visits are counted from this date.
3. Only women in Arms 3.2 and 3.3 who meet the requirements for breast milk transfer PK sampling will complete the 5-9 Days and 16-24 Weeks Visits, see [Section 6.10.4](#).
4. For women entering the study during the third trimester only.

5. See [Section 6.10.1](#)
6. Measured at the pharmacology laboratory from PK pre-dose sample.
7. See [Section 6.10.2](#).
8. Only applicable to arms 3.2 and 3.3. See [Section 6.10.4](#).
9. For women who meet the requirements for breast milk transfer PK sampling only, see [Section 6.10.4](#).
10. For women who have consented to genetic testing only, see [Section 6.11](#).
11. Initial PK sampling should be targeted to be performed within 5 days of enrollment but must be performed no later than 14 days after enrollment.

## Appendix I-D

### Maternal Schedule of Evaluations for Component 4: Pregnant WLHIV and HIV-uninfected women receiving Second-line TB Treatment

MATERNAL EVALUATIONS: COMPONENT 4	Screening	2 <sup>nd</sup> Trimester / Entry <sup>1</sup>	3 <sup>rd</sup> Trimester / Entry <sup>1</sup>	Delivery <sup>2</sup>	Post-Delivery <sup>2</sup>		
					5-9 Days (Breast milk transfer PK women only) <sup>3</sup>	2-8 Weeks	16-24 Weeks (Breast milk transfer PK women only) <sup>3</sup>
Visit Window	-60 days	20 0/7-26 6/7 weeks of pregnancy	30 0/7-37 6/7 weeks of pregnancy	+/- 4 days	5-9 days	14-62 days	112-174 days
Informed Consent	X						
<b>CLINICAL</b>							
Medical and Medication History	X	X	X	X	X	X	X
Abbreviated Physical Exam		X	X	X	X	X	X
<b>LABORATORY</b>							
Confirmatory HIV testing [if needed]	[0-6 mL]						
Chemistries		5 mL	5 mL	5 mL		5 mL	
Hematology		1 mL	1 mL	1 mL		1 mL	
<b>IMMUNOLOGY</b>							
CD4 cell count <sup>4</sup>		[1 mL]	[1 mL] <sup>5</sup>				
<b>VIROLOGY</b>							
HIV RNA <sup>4</sup>		[6 mL]	[6 mL]	[6 mL]		[6 mL]	
<b>PHARMACOLOGY</b>							
Intensive PK sampling (TB) <sup>6</sup>		17-19 mL <sup>13</sup>	17-19 mL <sup>13</sup>			17-19 mL	
Intensive PK sampling (ARV) <sup>6,7</sup>		[14-16 mL] <sup>13</sup>	[14-16 mL] <sup>13</sup>			[14-16 mL]	
Alpha-1 acid glycoprotein <sup>8</sup>		X	X			X	
Single PK sample				5 mL <sup>9</sup>	2-4 mL <sup>10</sup>		2-4 mL <sup>10</sup>
Cord blood PK sample <sup>9</sup>				X			
Breast milk PK sample <sup>10</sup>					5-10 mL	[5-10 m] <sup>11</sup>	5-10 mL
DBS storage for pharmacogenetics <sup>12</sup>		X	[X] <sup>5</sup>				
<b>TOTAL MAXIMUM BLOOD VOLUME</b>	<b>6 mL</b>	<b>48 mL</b>	<b>48 mL</b>	<b>17 mL</b>	<b>4 mL</b>	<b>47 mL</b>	<b>4mL</b>

[ ] indicate procedures that are not required for ALL participants at the specified visit.

#### APPENDIX I-D FOOTNOTES

- Entry may occur at the 2<sup>nd</sup> or 3<sup>rd</sup> trimester visit. Women entering the study at the 2<sup>nd</sup> trimester visit will also complete the 3<sup>rd</sup> trimester visit procedures.
- Day of delivery is defined as Day 0 and all post-delivery follow-up visits are counted from this date.
- Only women who meet the requirements for breast milk transfer PK sampling will complete the 5-9 Days and 16-24 Weeks Visits, see [Section 6.10.4](#).
- For WLHIV only.
- For women entering the study during the third trimester only.
- See [Section 6.10.1](#)

7. For WLHIV AND who are taking one or more of the ARVs under study for Component 4, as specified in [Table 1](#). See [Section 6.10.1](#)
8. Measured at the pharmacology laboratory from PK pre-dose sample.
9. See [Section 6.10.2](#).
10. See [Section 6.10.4](#). For WLHIV who are taking one or more of the ARVs under study for Component 4, as specified in [Table 1](#), a 10 mL breast milk sample will be collected (5 mL for TB drugs and 5 mL for ARVs), and a 4 mL blood sample will be collected (2 mL for TB drugs and 2 mL for ARVs). For women NOT on ARVs under study for Component 4, a 5 mL sample of breast milk and a 2 mL blood sample will be collected.
11. For women who meet the requirements for breast milk transfer PK sampling only, see [Section 6.10.4](#).
12. For women who have consented to genetic testing only, see [Section 6.11](#)
13. Initial PK sampling should be targeted to be performed within 5 days of enrollment but must be performed no later than 14 days after enrollment.



**Appendix I-E**  
**Maternal Schedule of Evaluations for Component 5: Postpartum WLHIV Breastfeeding while receiving Oral ARVs**

MATERNAL EVALUATIONS: COMPONENT 5	Screening	5-9 Days / Entry <sup>1</sup>	2-12 Weeks <sup>1</sup>	16-24 Weeks <sup>1</sup>
<i>Visit Window</i>	-60 days	5-9 days	14-90 days	112-174 days
Informed Consent	X			
<b>CLINICAL</b>				
Medical and Medication History	X	X	X	X
Abbreviated Physical Exam		X	X	X
<b>LABORATORY</b>				
Confirmatory HIV testing [if needed]	[0-6 mL]			
<b>PHARMACOLOGY<sup>2</sup></b>				
Single PK sample		2 mL	2 mL	2 mL
Breast milk sample		5 mL	5 mL	5 mL
DBS storage for pharmacogenetics <sup>3</sup>		X		
<b>TOTAL MAXIMUM BLOOD VOLUME</b>	<b>6 mL</b>	<b>2 mL</b>	<b>2 mL</b>	<b>2 mL</b>

[ ] indicate procedures that are not required for ALL participants at the specified visit.

**APPENDIX I-F FOOTNOTES**

- Day of delivery is defined as Day 0 and all follow-up visits are counted from this date. Only mother-infant pairs who continue meet the requirements for breast milk transfer PK sampling per [Section 6.10.4](#) will complete these visits. Mother-infant pairs who no longer meet breast milk transfer PK sampling requirements will come off study.
- Blood and breast milk sample collection shown in this schedule are applicable to a single Component 5 Arm. For mother-infant pairs who are contributing data to multiple Component 5 Arms in parallel, the sample collection schedule must be applied to each Arm the mother-infant pair is contributing to.
- For women who have consented to genetic testing only, see [Section 6.11](#)

**Appendix II-A**  
**Infant Schedule of Evaluations: Infants in Components 1, 3 and 4**

<b>INFANT EVALUATIONS: COMPONENTS 1, 3 and 4</b>	<b>Birth<sup>1</sup></b>	<b>5-9 Days<sup>2</sup></b> <i>(Washout and/or breast milk transfer PK infants only)</i>	<b>2-8 Weeks<sup>3</sup></b> <i>(Breast milk transfer PK infants only)</i>	<b>16 – 24 Weeks</b>
<i>Visit Window</i>	0 – 3 days	5-9 days	14 – 62 days	112 – 174 days
<b>CLINICAL</b>				
Abbreviated Physical Exam	X	X	X	X <sup>4</sup>
Medical and Medication History	X	X	X	X <sup>4</sup>
Infant Feeding History	X	X	X	X <sup>4</sup>
<b>PHARMACOLOGY</b>				
Washout PK sample <sup>5</sup>	[2.25 mL]	0.75 mL		
Breast milk transfer PK sample <sup>6</sup>		X <sup>2</sup>	0.75-1.5 mL	[0.75-1.5 mL]
DBS storage for pharmacogenetics <sup>7</sup>	[0.25 mL]	[0.25 mL]		
<b>TOTAL MAXIMUM BLOOD VOLUME</b>	<b>2.5 mL</b>	<b>1 mL</b>	<b>1.5 mL</b>	<b>1.5 mL</b>

[ ] indicate procedures that are not required for ALL participants at the specified visit.

**APPENDIX II-A Footnotes:**

1. Day of birth is defined as Day 0 and all follow-up visits are counted from this date.
2. Only infants who meet the requirements for infant washout PK sampling (see [Section 6.10.3](#)) will have a 5-9 Days visit. For infants who also meet the requirements for breast milk transfer PK sampling (see [Section 6.10.4](#)), drug concentrations for breast milk transfer PK assessments will be measured from the washout PK sample at these visits.
3. Only infants who meet the requirements for breast milk transfer PK sampling (see [Section 6.10.4](#)) will have a 2-8 Weeks visit.
4. For infants NOT undergoing breast milk transfer PK sampling, the allowable visit window for these procedures is extended to 204 days.
5. For infants who meet the requirements for infant washout PK sampling only, see [Section 6.10.3](#).
6. For infants meeting requirements for breast milk transfer PK only, see [Section 6.10.4](#). Blood volumes drawn at these visits are determined based on the drug(s) under study and are specified in the LPC.
7. For infants who meet the requirements for infant washout PK sampling (see [Section 6.10.3](#)) AND for whom consent for genetic testing has been obtained, see [Section 6.11](#); collect once, at Birth OR the 5 – 9 Days visit.

**Appendix II-B**  
**Infant Schedule of Evaluations: Infants in Component 2**

<b>INFANT EVALUATIONS: COMPONENT 2</b>	<b>Birth<sup>1</sup></b>	<b>5-9 Days<sup>2</sup></b> <i>(Washout and/or breast milk transfer PK infants only)</i>	<b>12-16 Days<sup>2</sup></b> <i>(Washout and/or breast milk transfer PK infants only)</i>	<b>3-5 Weeks<sup>3</sup></b> <i>(Breast milk transfer PK infants only)</i>
<i>Visit Window</i>	0- 3 Days	5-9 Days	12-16 Days	21 – 41 days
<b>CLINICAL</b>				
Abbreviated Physical Exam	X	X	X	X
Medical and Medication History	X	X	X	X
Infant Feeding History	X	X	X	X
<b>PHARMACOLOGY</b>				
Washout PK sampling <sup>4</sup>	[2.25 mL]	0.75 mL	0.75 mL	
Breast milk transfer PK sampling <sup>5</sup>		X <sup>2</sup>	X <sup>2</sup>	0.75 mL
DBS storage for pharmacogenetics <sup>6</sup>	[0.25 mL]	[0.25 mL]		
<b>TOTAL MAXIMUM BLOOD VOLUME</b>	<b>2.5 mL</b>	<b>1 mL</b>	<b>0.75 mL</b>	<b>0.75 mL</b>

[ ] indicate procedures that are not required for ALL participants at the specified visit.

**APPENDIX II-B Footnotes:**

1. Day of birth is defined as Day 0 and all follow-up visits are counted from this date.
2. Only infants who meet the requirements for infant washout PK sampling (see [Section 6.10.3](#)) will have 5-9 Days and 12-16 Days visits. For infants who also meet the requirements for breast milk transfer PK sampling (see [Section 6.10.4](#)), drug concentrations for breast milk transfer PK assessments will be measured from the washout PK sample at these visits.
3. Only infants who meet the requirements for breast milk transfer PK sampling (see [Section 6.10.4](#)) will have 3-5 Weeks visit.
4. For infants who meet the requirements for infant washout PK sampling only, see [Section 6.10.3](#).
5. For infants who meet the requirements for breast milk transfer PK only, see [Section 6.10.4](#).
6. For infants who meet the requirements for infant washout PK sampling (see [Section 6.10.3](#)) AND for whom consent for genetic testing has been obtained, see [Section 6.11](#); collect once, at Birth OR the 5 – 9 Days visit.

**Appendix II-C**  
**Infant Schedule of Evaluations: Infants in Component 5**

INFANT EVALUATIONS: COMPONENT 5	Screening	5-9 Days / Entry <sup>1</sup>	2-12 Weeks <sup>1</sup>	16-24 Weeks <sup>1</sup>
<i>Visit Window</i>	-60 days	5-9 days	14-90 days	112-174 days
<b>CLINICAL<sup>7</sup></b>				
Abbreviated Physical Exam		X	X	X
Medical and Medication History		X	X	X
Infant Feeding History		X	X	X
<b>PHARMACOLOGY</b>				
Breast milk transfer PK sampling <sup>2</sup>		0.75 mL	0.75 mL	0.75 mL
DBS storage for pharmacogenetics <sup>3</sup>		[0.25 mL]		
<b>TOTAL MAXIMUM BLOOD VOLUME</b>		<b>1 mL</b>	<b>.75 mL</b>	<b>.75 mL</b>

[ ] indicate procedures that are not required for ALL participants at the specified visit.

APPENDIX II-C Footnotes:

1. Day of birth is defined as Day 0 and all follow-up visits are counted from this date. Only mother-infant pairs who continue meet the requirements for breast milk transfer PK sampling per [Section 6.10.4](#) will complete these visits. Mother-infant pairs who no longer meet breast milk transfer PK sampling requirements will come off study.
2. See [Section 6.10.4](#).
3. For infants of mothers who have consented to genetic testing only, see [Section 6.11](#).

## Appendix III: Dietary Recommendations for ARV and TB Drugs

### NRTIs

- Tenofovir alafenamide (TAF): Take with a meal.

### PIS/COMBINATIONS

- Darunavir/ritonavir twice daily: Take with food to enhance bioavailability. Studied with meals ranging from 240 Kcal (12 grams of fat) to 928 Kcal (56 grams of fat).
- Lopinavir/ritonavir (Alluvia<sup>®</sup>): Take with a high fat meal to enhance bioavailability and minimize pharmacokinetic variability. (Studied with meals of ~850 Kcal, ~55% from fat.)
- Atazanavir/ritonavir: Take with a light meal to enhance bioavailability and minimize pharmacokinetic variability. Take at least two hours before or one hour after administration of an antacid.

### NNRTIs

#### Integrase Inhibitors

- Dolutegravir: May be taken without regard to meals.

#### First Line Tuberculosis Drugs:

If a combination product is used, then it should be administered with food. If administered as separate medications:

- Ethambutol: Take with food to minimize stomach upset if needed.
- Isoniazid: Take on an empty stomach (at least one hour before or two hours after a meal)
- Pyrazinamide: May be administered without regard to meals.
- Rifampicin: Take on an empty stomach (at least one hour before or two hours after a meal).

#### Second Line Tuberculosis Drugs:

Second Line TB treatment drugs can be given without regards for meals, with the exception of delamanid and bedaquiline which should be administered with meals.

**Appendix IV:  
Maternal Intensive and Sparse PK Sampling Schedules for Components 1, 3, and 4**

**Appendix IV-A. Intensive PK Evaluation Sampling Time Points**

ARMS	Type of PK	REGIMEN(S) BEING STUDIED	PK SAMPLING SCHEDULE, TIME POINTS, and VOLUME	
ARM	Type of PK as Indicated in Schedule of Evaluations	COMPONENT 1: ARVS WITHOUT TB DRUGS <i>Sampling during 2<sup>nd</sup> Trimester, 3<sup>rd</sup> Trimester, and 6-12 Weeks Post-Delivery PK Visits, per Appendix I-A.</i>	Intensive PK 24-hr sampling <i>(Collect all samples within 30 minutes on either side of scheduled collection time)</i>	Intensive PK 12-hr sampling <i>(Collect all samples within 30 minutes on either side of scheduled collection time)</i>
1.1	Intensive PK (non-TAF ARV)	Bictegravir 50 mg q.d.	5 mL pre-dose; 2 mL at 1, 2, 4, 6, 8, 12, and 24 hours post-dose	n/a
1.2		Doravirine 100 mg q.d.	5 mL pre-dose; 2 mL at 1, 2, 4, 6, 8, 12, and 24 hours post-dose	n/a

ARMS	Type of PK	REGIMEN(S) BEING STUDIED	PK SAMPLING SCHEDULE, TIME POINTS, and VOLUME	
<b>ARM</b>	<b>Type of PK as Indicated in Schedule of Evaluations</b>	<b>COMPONENT 3: ARVS AND FIRST-LINE TB TREATMENT DRUGS</b> <i>Sampling during 2<sup>nd</sup> Trimester (optional), 3<sup>rd</sup> Trimester, and 2-8 Weeks Post-Delivery PK Visits, per Appendix I-C.</i>	<b>Intensive PK 24-hr sampling</b> <i>(Collect all samples within 30 minutes on either side of scheduled collection time)</i>	<b>Intensive PK 12-hr sampling</b> <i>(Collect all samples within 30 minutes on either side of scheduled collection time)</i>
3.1	Intensive PK (ARV)	Dolutegravir 50 mg b.i.d. (when combined with RIF) <b>OR</b>	n/a	2 mL pre-dose and at 1, 2, 4, 6, 8, and 12 hours post-dose
		Dolutegravir 50 mg q.d. (if RIF is not part of the TB regimen)	2 mL pre-dose and at 1, 2, 4, 6, 8, 12, and 24 hours post-dose	
3.2		Atazanavir/ritonavir ≥ 300/100 mg q.d. <b>OR</b>	2 mL pre-dose and at 1, 2, 4, 6, 8, 12, and 24 hours post-dose	n/a
		Darunavir/ritonavir ≥ 600/100 mg b.i.d.	n/a	2 mL pre-dose and at 1, 2, 4, 6, 8, and 12 hours post-dose
3.3		Lopinavir/ritonavir 800/200 mg b.i.d.	n/a	2 mL pre-dose and at 1, 2, 4, 6, 8, and 12 hours post-dose
3.1, 3.2, and 3.3	Intensive PK (TB)	First-line TB treatment drugs: Isoniazid 4-6 mg/kg q.d.; Rifampin 8-12 mg/kg q.d.; Rifabutin 150-300 mg q.d.; Ethambutol 15-20 mg/kg q.d.; Pyrazinamide 20-30 mg/kg q.d.; Moxifloxacin 400 mg or 800mg q.d.	<b><i>If also on ATV/r:</i></b> 5 mL pre-dose; 2 mL and at 1, 2, 4, 6, 8, 12, and 24 hours post-dose	<b><i>If not on ATV/r:</i></b> 5 mL pre-dose; 2 mL at 1, 2, 4, 6, 8, and 12 hours post-dose

ARMS	Type of PK	REGIMEN(S) BEING STUDIED	PK SAMPLING SCHEDULE, TIME POINTS, and VOLUME	
<b>ARM</b>	<b>Type of PK as Indicated in Schedule of Evaluations</b>	<b>COMPONENT 4: SECOND-LINE TB TREATMENT DRUGS with or without ARVs</b> <i>Sampling during 2<sup>nd</sup> Trimester (optional), 3<sup>rd</sup> Trimester, and 2-8 Weeks Post-Delivery PK Visits, per Appendix I-D.</i>	<b>Intensive PK 24-hr sampling</b> <i>(Collect all samples within 30 minutes on either side of scheduled collection time)</i>	<b>Intensive PK 12-hr sampling</b> <i>(Collect all samples within 30 minutes on either side of scheduled collection time)</i>
4.1	Intensive PK (TB)	Second-line TB treatment drugs: Moxifloxacin 400mg or 800mg q.d. or levofloxacin 750mg – 1000mg q.d.; Clofazimine 100mg q.d.; Linezolid 300mg – 600mg q.d.; Bedaquiline 200mg t.i.w.; Delamanid 100mg b.i.d.	<b><i>If also on EFV or ATV/r:</i></b> 5 mL pre-dose; 2 mL at 1, 2, 4, 6, 8, 12, and 24 hours post-dose	<b><i>If <u>not</u> on EFV or ATV/r:</i></b> 5 mL pre-dose; 2 mL at 1, 2, 4, 6, 8, and 12 hours post-dose
	Intensive PK (ARV)	If also on ARVs: EFV, ATV/r	5 mL pre-dose; 2 mL at 1, 2, 4, 6, 8, 12, and 24 hours post-dose	n/a
		If also on ARVs: DTG, DRV/r, LPV/r	n/a	5 mL pre-dose; 2 mL at 1, 2, 4, 6, 8, and 12 hours post-dose



**Appendix IV-B. Sparse PK Evaluation Sampling Time Points**

ARMS	Type of PK	REGIMEN(S) BEING STUDIED		
<b>ARM</b>	<b>Type of PK as Indicated in Schedule of Evaluations</b>	<b>COMPONENT 1: ARVS WITHOUT TB DRUGS</b> <i>Sampling during 2<sup>nd</sup> Trimester, 3<sup>rd</sup> Trimester, and 6-12 Weeks Post-Delivery PK Visits, per Appendix I-A.</i>		
1.3	Sparse PK	Tenofovir alafenamide - 10 mg q.d. boosted with cobicistat		
1.4		Tenofovir alafenamide - 25 mg q.d. without boosting		
1.5		Tenofovir alafenamide - 25 mg q.d. boosted with cobicistat or ritonavir		
<b>SPARSE PK SAMPLING SCHEDULE:</b>				
<b>Time Points</b>	<b>Pre-dose</b>	<b>0.5 hrs post-dose</b>	<b>3 hrs post-dose</b>	<b>24 hrs post-dose</b>
<b>Window</b>	No window	±15 mins	±1 hr	±2 hours
<b>Volumes</b>	2 mL (Plasma and DBS)	5 mL (Plasma only)	2 mL (Plasma only)	2 mL (Plasma only)
	6 mL (PBMC)		6 mL (PBMC)	6 mL (PBMC)

hr(s)=hour(s); mins=minutes

**Appendix V:  
Maternal PK Parameter Targets**

<b>ARV Under Study</b>	<b>PK Parameter</b>	<b>Non-pregnant Typical Value (mcg*hr/mL)</b>	<b>Estimated 10<sup>th</sup> percentile (mcg*hr/mL)</b>	<b>Reference</b>
Bictegravir 50 mg q.d.		102 mg*h/L	58.7 mg*h/L	Biktarvy package insert dated Feb 2018  Gallant JE, et al. J Acquir Immune Defic Syndr 2017 May 1;75(1):61-66.
Doravirine 100 mg q.d.		16.1 mg*h/L	10.0 mg*h/L	Delstrigo package insert dated Aug 2018  Yee KL et al. Antimicrob Agents Chemother 63:e02502-18. <a href="https://doi.org/10.1128/AAC.02502-18">https://doi.org/10.1128/AAC.02502-18</a> < <a href="https://doi.org/10.1128/AAC.02502-18">https://doi.org/10.1128/AAC.02502-18</a> >>.
Dolutegravir 50 mg b.i.d.	AUC <sub>0-24</sub>	53.6	37.5*	Tivicay™ [package insert] Research Triangle Park, NC; ViiV Healthcare; 2014
Atazanavir/ritonavir ≥ 300/100 mg q.d	AUC <sub>0-24</sub>	57	29.4	Reyataz™ [package insert] Princeton, NJ; BMS Virology; 2003.
Darunavir/ritonavir ≥ 600/100 mg b.i.d.	AUC <sub>0-12</sub>	62.3	43.6*	Prezista™ [package insert] Titusville, NJ; Janssen; 2012
Lopinavir/ritonavir 800/200 mg b.i.d.	AUC <sub>0-12</sub>	80	52	Murphy R, Brun S, Hicks C, Eron J, Gulick R, King M, et al. ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naïve adults with HIV-1 infection: 48-week results. AIDS 2001;15: 1-9.

\* There are inadequate data for this combination to estimate the 10<sup>th</sup> percentile. Therefore, a 30% reduction from typical exposure will be used as the minimal acceptable exposure.

## Appendix VI: Sample Informed Consent Forms

### Appendix VI-A Part 1: MASTER Sample Informed Consent Form for Participation in Component 1

*[U.S. sites may NOT modify Part 1]*

#### PART 1: MASTER INFORMED CONSENT FORM

##### IMPAACT 2026

##### Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum

Version 1.0, 22 January 2020

#### ***Introduction***

You and your baby are being asked to take part in the research study named above because you are pregnant and taking one or more of the following HIV medicines: **bictegravir, doravirine, and/or tenofovir alafenamide (TAF)**.

This consent form gives information about the study. Please read it, or have it read to you, and ask any questions you may have. You may have as much time as needed to fully understand the study. We will ask you questions to see if we have explained the study clearly.

This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study, this informed consent form includes two parts. Part 1 of the consent form includes general study information that applies to all study sites. Part 2 of the consent form includes information specific to the study site where you are being asked to enroll. Before making your decision, both parts of this form will be reviewed with you. You will have the opportunity to discuss any questions about this form and both of its parts with your site's study team.

#### ***Key Information***

Here is a summary of important information about the study:

- The primary purpose of the study is to determine how much HIV medicine is in a woman's blood during pregnancy. Another purpose is to look at how much HIV medicine gets into her baby after delivery, and how safe the medicines are for mother and baby.
- If you choose to join the study, you will have your first visit during the second or third trimester of your pregnancy and will stay in the study for at least 3 months after you deliver. You will have one or two study visits while you are pregnant, a study visit at delivery and at least one study visit after your baby is born.
- Your baby will be in the study for about 6 months after birth. Your baby will have at least three study visits.
- You will continue to receive the HIV treatment medicines given by your health care provider.
- You will have blood drawn at each study visit to measure the amount of HIV medicine in your blood, and your baby may have blood drawn at each visit too.

- You will be asked questions about your and your baby's health and you and your baby will have physical exams and routine blood tests. You will also have blood drawn to check the amount of HIV in your blood.
- There may be no direct benefit to you or your baby from being in the study. However, this study may help doctors learn information that will help in the treatment of future patients with HIV.
- The most likely risk to you and your baby is from blood drawing- including pain, which is usually minor, and infection, which is rare.
- Your decision will have no effect on the medical care that you and your baby would normally receive from your clinic. Your access to services, and the benefits and rights you normally have, will not be affected.

More information is given in both parts of this form about the study, its risks and benefits. You should feel that you understand the study before deciding whether you and your baby will participate. After you understand the study, and if you decide that you and your baby will join the study, you will be asked to sign or make your mark on this form. You will be offered a copy to keep. You do not give up any rights by signing this form.

### ***About the study***

This study is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT).

The study will measure the amounts of different HIV medicines in the blood of pregnant women and their babies. The study will include up to 28 mothers and their babies for each medicine or combination of medicines that we are looking at, from Botswana, Brazil, India, Kenya, Malawi, South Africa, Tanzania, Thailand, Uganda, Zimbabwe, and the United States. You and your baby will be in the study through your pregnancy and for up to 24 weeks after your baby is born.

The United States National Institutes of Health are paying for this study.

#### **1. The study will measure the amounts of HIV medicines in the blood of pregnant women and their babies.**

The amount of HIV medicines needed during pregnancy to treat your HIV infection and to protect your baby from HIV infection while being safe for you and your baby has not been studied for all HIV medicines. In this study, we will compare levels of HIV medicines in pregnant women to levels in non-pregnant adults on the same medicines. The amount of medicine found in blood from your baby's umbilical cord will be compared to the amount of medicine in your blood at the time of delivery. We will also look to see how much of the HIV medicine you took while you were pregnant got into your baby's blood after your baby was born, and how safe these medicines are for you and your baby.

#### **2. Only pregnant women who are eligible can join the study.**

If you decide to join the study with your baby, we will first talk to you about the study and collect some information about you to find out if you are eligible. More information about this is given in section #4 below. If you are eligible, you can join the study. If you are not eligible, you cannot join the study.

#### **3. It is your decision whether or not you join the study.**

Deciding to join the study is voluntary (your choice). If you are eligible, you can choose if you want to join the study or not. You are free to join or not join. If you join, you must agree for your baby to join the study too. If you and your baby join, you can change your mind later and leave the study. Your decision will have no effect on the

medical care that you and your baby would normally receive from your clinic. Your access to services, and the benefits and rights you normally have, will not be affected. If you decide to join, we will tell you any new information from this study or other studies that may affect your willingness to stay in the study. You are welcome to ask questions or request more information at any time.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. You can bring other people here to learn about the study with you.

#### ***Finding out if You and Your Baby are Eligible for the Study***

#### **4. We will ask you questions, look at your medical records, and discuss the study with you.**

You will need to come to the clinic to make sure you are eligible for the study before you join. This may be done as part of your first study visit or during a routine care visit, so a separate visit may not be required. To find out if you can join, we will talk to you about what you will have to do if you decide to join the study. We will collect some information from your medical records about you, your health, your pregnancy, and the medications that you take. We may test your blood for HIV to confirm your status. If we test your blood for HIV, we will give you the results. We will tell you if you are or are not eligible for the study.

#### ***Entering the study***

#### **5. If you are eligible, you will enter the study during your second or third trimester.**

Women can only join the study when they are 20-26 weeks pregnant or 30-37 weeks pregnant. If you are eligible, we will tell you when it is the right time to enter the study. You will also need to be on your HIV medicines for at least 2 weeks before your first study visit.

#### ***Being in the study***

#### **6. You will continue to take your HIV medicines.**

If you join the study, you will continue to receive and take your HIV medicines as you normally would. No HIV medicines are supplied by this study. It will be important for you to continue with all of your regular HIV care even if you join the study.

#### **7. You will have up to two study visits during your pregnancy and at least one study visit after giving birth.**

If you enroll in the study during your second trimester, you will have a study visit when you are 20-26 weeks pregnant, a study visit when you are 30-37 weeks pregnant, and a study visit 6-12 weeks after you give birth. If you enroll during your third trimester, you will only have one visit during your pregnancy when you are 30-37 weeks pregnant, as well as the visit 6-12 weeks after you give birth.

At each visit, we will ask you about your health, do a physical exam, and do routine blood tests. We will also draw blood to check how well your body is able to fight infection and to check the amount of HIV in your blood. The total amount of blood drawn for these tests is about 13 mL (2 ½ teaspoons). You will be given the results of these tests. At each visit you will be asked about taking your medicines.

At each visit, repeat blood samples will also be drawn to measure the amount of HIV medicine in your blood. A small plastic catheter (soft tube) will be placed in a vein in your arm during this visit, so that blood can be drawn multiple times, without having to stick you with a needle several times. The tube may stay in place until all of the blood samples are drawn.

- If you are taking **bictegravir** or **doravirine**, 8 blood samples over 24 hours will be drawn. Each time, we will draw 2 mL (less than 1 teaspoon) of blood, for a total of 19 mL (about 4 teaspoons).
- If you are taking **TAF**, 4 blood samples over 24 hours will be drawn. Each time, we will draw between 2-8 mL of blood (less than 1 teaspoon to about 2 teaspoons), for a total of 29 mL (about 6 teaspoons) of blood.

For three days before your visit, you must be sure to take your medicines at the same time each day, but you must **not** take your HIV medicine(s) on the day you come to the clinic for your study visit. This is very important. We will help you remember this before the visit.

When you come to the visit, we will place a small catheter (soft tube) into your arm and draw your first blood sample, then you will take your HIV medicine(s), and then we will collect the rest of your blood samples over 24 hours from the same catheter so we can avoid multiple pokes during the day. You will be asked to tell us the times of your previous two doses of medicines and to describe the time and amount of your previous two meals. Before these repeat blood samples are drawn, the study staff will review with you any dietary recommendations related to the HIV medicines you are taking.

If you have blood samples collected over 24 hours, you may be permitted to remain in the clinic overnight, or you may be able to leave the clinic after your last blood draw before the 24 hour blood draw, in which case you must return for the 24 hour blood draw at the time the clinic tells you to return. Part 2 of this form provides more information about what will happen for you at this clinic.

While you are pregnant, if you are taking **bictegravir** or **doravirine**, once your HIV medicine levels have been determined they will be reported back to you and your doctor as soon as possible. If these levels are low compared to those in non-pregnant adults, you and your doctor will be told. You may decide, in consultation with your doctor, to adjust the dose of the medicine(s). If you and your doctor choose to change your dose of medicine, you may choose to have your blood checked for medication levels on your new dose of medication. After you give birth, the medicine levels testing will be done in batches later in the study, so you and your doctor won't get results of these tests.

If you are taking **TAF**, the results of your HIV medicine levels will not be reported back to you at any time because these tests will be done later in the study.

In addition to these visits, there will also be a study visit at the time of delivery (see #8 below) and visits for your baby (see #9 below).

#### **8. You will have a study visit at the time of delivery.**

At or near the time of delivery, we will ask you questions about your health, do a physical exam, and do routine blood tests. Blood will also be drawn to check how well your body is able to fight infection, to check the amount of HIV in your blood, and to measure the amount of HIV medicines in your blood.

- If you are taking **bictegravir** or **doravirine**, a total of about 17 mL (about 3 ½ teaspoons) of blood will be drawn from you.
- If you are taking **TAF**, a total of about 23 mL (about 4 ½ teaspoons) of blood will be drawn from you.

Right after your baby is born, a small amount of blood will also be drawn from the umbilical cord that is attached to the placenta after the cord is clamped. This will be used to measure the amount of medicines that get into your baby's blood, but this blood comes from the placenta, and not from your baby. You will be given the results of all

tests, except the tests to measure the amount of HIV medicines in your blood and the blood from your umbilical cord.

**9. Your baby will have study visits after birth.**

After your baby is born, your baby will be examined 3 times during the study: from birth to 3 days after birth, 5-9 days after birth, and at 4-6 months of age. During these visits, your baby will be weighed and measured and information about your baby's health will be recorded from his/her medical records. If your baby is healthy enough, we will also collect some blood samples to determine how much of the HIV medication(s) that you took during pregnancy got into your baby and how long after birth they are present in your baby's blood. We will ask you about how you feed your baby. Your baby will have blood samples drawn 3 times between birth and 3 days old, and a fourth sample drawn between 5 and 9 days after birth. About 1 mL (less than ¼ teaspoon) of blood will be drawn for each sample. The total amount of blood collected for these tests will be around 4 mL (less than 1 teaspoon). These tests will be done later so you will not receive the results of these tests.

Each of your baby's study visits will last about 30 minutes to 1 hour.

**10. Different tests will be done at different laboratories**

We will test some of your samples to check your health at our laboratory. Tests to determine the amount of medicine in your samples or your baby's samples will be done at other laboratories that have special tests for this. Samples for these special tests may be sent to laboratories in other countries.

**11. If you agree, some of your and your baby's blood will be used for genetic testing.**

If you agree, we will use some of your blood for genetic testing. Also, if you agree, we will collect one drop of blood for genetic testing of your baby. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people break down medicines differently and this can change the levels of the medicines in their bodies. If you agree, your and your child's blood would only be used to look at differences in specific genes that may affect the levels of some medicines. Testing of all of your or your child's genes, which is sometimes called whole genome sequencing, will not be done. You may decide that you do not want genetic testing for you or your baby. You may change your decision about having genetic testing at any time by contacting the study clinic. You can still join in this study even if you do not agree to genetic testing. This test will be done later in the study, so you will not receive the results of this test, and the results will not go into your medical records or have your name attached to them.

**Please write your initials or make your mark below to indicate your decision about genetic testing.**

<p><b>For YOUR optional genetic testing:</b></p> <p>_____ I agree to allow testing of my genes that can affect the levels of medicines in the body.</p> <p>_____ I do not agree to allow testing of my genes.</p> <p><b>For YOUR BABY'S optional genetic testing:</b></p> <p>_____ I agree to allow testing of my baby's genes that can affect the levels of medicines in the body.</p> <p>_____ I do not agree to allow testing of my baby's genes.</p>
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**12. We may take you or your baby off of the study early.**

The study doctor may need to take you and your baby off the study early without your permission if:

- The study is stopped for any reason.
- You are/your baby is not able to attend the study visits as required by the study.
- We determine that staying in the study might harm you or your baby.

If you must stop taking the HIV medicine(s) before the study is over, we may ask you to continue to be part of the study and return for the scheduled study visits and some of the procedures. If you stop the study HIV medicines, we may also ask that your baby stay in the study and complete the scheduled study visits and some of the procedures as described in #9 above.

**13. Please tell us if you want to leave the study.**

You and your baby are free to leave the study at any time for any reason. The care that you receive at this clinic will not be affected, but it is important for us to know about your decision.

***Risks of the study***

Taking part in this study may involve some risks and discomfort.

**14. Risk from blood draws**

Blood drawing may cause fainting, lightheadedness or some discomfort. Other risks include bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or swelling of the surrounding skin may occur. There is also a small risk of a minor infection at the blood draw site. Blood drawing from your baby can also be done by heel stick. Heel stick may cause some discomfort, bleeding or bruising at the site of the heel stick. There is a small risk of infection at the site of the heel stick.

**15. There could be risks of disclosure of your information.**

We will make every effort to keep your and your baby's information private and confidential. Study records and specimens will be kept in secure, locked locations. All specimens and most records will be labeled only with a code number. However, your name will be written on some records.

Despite our best efforts to keep your information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stress or embarrassment.

***Benefits of the study***

**16. There may be no direct benefit to you or your baby from being in the study.**

If you take part in this study, there may be no direct benefit to you or your baby. You may benefit from having the levels of HIV medicine(s) in your blood measured and having your blood checked for safety effects. Information learned from this study may help others who have HIV.

***Other information about the study***

**17. There are no costs from being in the study.**



There is no cost for the study-related clinic visits, examinations, and laboratory tests in this study.

**18. Study records may be reviewed by study staff and groups that oversee the study.**

Groups that oversee the study include:

- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your or your baby's name or identify you or your baby personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you or your baby. At most, the website will include a summary of the results. You can search this website at any time. If you want the results from this study, please tell the study staff.

Your or your baby's study information may be given to other authorities if required by law.

**19. What will happen with your data and specimens after the study.**

The samples collected from you and your baby will only be used for the testing described in this form. The samples will not be used for other research now or in the future. The samples will not be sold or used for commercial profit. For example, the samples will not be used to make a new product that could be sold.

Other information collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about HIV. Any future research done with the information from this study must be approved by the IMPAACT Network. If any future research is done, information about you or your baby may be used. Your or your baby's information will be labeled with a code number, and the only link between the code number and your name or your baby's name will be kept at this site. Your name or your baby's name will not be given to other researchers.

Data or information from the study may be shared with drug companies who have agreements with the IMPAACT Network and/or the U.S. NIH, or regulatory entities, but you or your baby will never be identified personally.

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

## Appendix VI-A Part 2: SITE-SPECIFIC Consent Information for Participation in Component 1

### PART 2: SITE-SPECIFIC CONSENT INFORMATION

**Site Name:**

**Study Title:** IMPAACT 2026: Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum, Version 1.0, 22 January 2020

JHM IRB Application Number: <<US sites only.>>

**Site Investigator of Record:**

**Site Principal Investigator Contact Information:**

**Emergency Contact:**

**Other Study Contact(s):**

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#### Introduction

This study is being done at multiple sites. This part of the consent form includes information about your site and is specific to participation at your site only. Before making your decision, both the site-specific information and general study information will be reviewed with you. You will have the opportunity to discuss any questions, including questions about this portion of the consent document, with your site's study team.

#### Site-Specific Study Procedures and Associated Risks

**Procedures for Repeat Blood Samples**

As described in Part 1 #7 of this form, we will collect repeat blood samples from you several times over 24 hours at up to two visits during your pregnancy and one visit after you give birth.

<<Sites should select one of the following descriptions of procedures for intensive PK blood samples collected over 24 hours, to clarify the information provided in #7 of Part 1 and to specify what will happen for participants at your site. Sites may modify the description if necessary, to further make site specific or provide any additional details relevant to the local context.>>

*Example 1:* For these visits, you will need to stay throughout the day and overnight at the clinic or hospital for up to 24 hours.

*Example 2:* For these visits, you will stay in the clinic or hospital through the second-to-last blood draw (the blood draw before your final blood draw at 24 hours), but you can go home after that and return to the clinic the next day for the final 24-hour blood draw. It is also possible to have room accommodations made within walking distance to the clinic or hospital for this visit.

**Costs to Study Participants:**

<<Brief description of costs to participants. Only include if different than costs as described in the main consent document. >>

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

*Example:* Any medical costs for your treatment outside this study, including your prescribed medicines for HIV, will be charged to you or your health insurance company. This study will not cover any cost related to your pregnancy and delivery or care of your baby.

### **Payment for Study Participation:**

<<Brief description of payments and/or reimbursements. >>>>

### **Compensation for Research-Related Injury:**

Your health is important to us. We will make every effort to protect your and your baby's well-being and minimize risks.

<<Add any locally-required language for research-related injury and contact information outlining who subjects should call in the event of any research-related injuries. Information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement about no compensation through the US NIH is mandatory for all sites and may not be deleted.>>

If you are/your baby is injured as a result of being in this study, you/your baby will be given immediate treatment for your/your baby's injuries. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation through the United States National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

### **Certificate of Confidentiality**

<<U.S. SITES only MUST include, sites outside of the U.S. MUST delete Certificate of Confidentiality section:>>

To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify you or your baby, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you or your baby. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

### **Contact Information:**

***If you have questions, concerns, or problems at any time, use these contacts.***

- If you have questions about the study:  
<< insert name and telephone number of investigator or other study staff >>
- If you or your baby have any health or other problems that may be related to study participation:  
<< insert name and telephone number of investigator or other study staff >>
- If you want to leave the study:  
<< insert name and telephone number of investigator or other study staff >>

**Do not use this form for consenting research participants unless a stamp appears here.**

*<<US sites only.>>*

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

- *<< Non-U.S. sites should modify the following as appropriate.>>* This study has been reviewed by an Institutional Review Board (IRB), a group of people that reviews human research studies. The IRB protects the rights and welfare of the people taking part in those studies. The IRB can help you if you have questions about your or your child's rights as a research participant or if you have other questions, concerns or complaints about this research study. If you have questions about your or your baby's rights as research participants or concerns about how you are/your baby is being treated in the study:
  - For this multi-site study, Johns Hopkins has agreed to serve as the single IRB (sIRB) providing oversight for all sites in the U.S. You may contact the Johns Hopkins IRB at **410-502-2092** or **jhmeirb@jhmi.edu** with your questions or concerns.
  - You may also contact the [*site specific IRB contact information*] with your questions or concerns. *<< If your site wishes to include local IRB contact information, please include this here. If this is not required, please delete this section. >>*

### **Additional information about your local site:**

*<<Please insert any additional required language for your site, as applicable for this study. Examples may include*

- *Local regulatory authorities that may review study records (in addition to those listed in Part 1 #18)*
- *Local language regarding state law requirements for reporting of communicable diseases or other mandated reporting requirements*
- *Locally required language for any specific research procedures, e.g. commercialization of cell lines*
- *Local conflict of interest disclosures*

### **How will your privacy be maintained and how will the confidentiality of your data be protected?**

*<< Insert locally-required HIPAA authorization language. The following language has already been approved by the JHM IRB. Please consider whether this language may be used at your site:*

- *If this language is acceptable, it may remain in this section.*
- *If this language is not acceptable, and locally-approved HIPAA authorization language is required, please delete the language and replace it with your own language.*
- *Alternatively, if your site requires use of a separate HIPAA authorization, please delete this section and include the following sentence: "[Add site name] requires that you sign a separate authorization form related to the use of your protected health information for this research study. This is required for participation in this study." >>*

### **HIPAA Authorization for Disclosure of Protected Health Information**

#### **What information is being collected, used, or shared?**

To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

#### **Who will see, use or share the information?**

The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at *<< insert site name >>*, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of *<< insert site name >>*. This may include the sponsor of the study

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

**Do you have to sign this Authorization?**

You do not have to sign this Authorization, but if you do not, you may not join the study.

**How long will your information be used or shared?**

Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

**What if you change your mind?**

You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

**Signature Lines:**

*<<US sites: If your site wishes to include site-specific signature lines, please include them here. If your site does not have site-specific signature requirements, the JHM IRB signature lines will be added in this section. Non-US sites: If your site wishes to include site-specific signature lines, please include them here. If your site does not have site-specific signature requirements, please use the template lines provided below. >>*

**If you agree to participate in this study, please sign or make your mark below.**

\_\_\_\_\_  
Name of Participant  
(print)

\_\_\_\_\_  
Signature of Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Study Staff Conducting  
Consent Process Name (print)

\_\_\_\_\_  
Signature of Study Staff

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Witness  
(as appropriate; print)

\_\_\_\_\_  
Signature of Witness

\_\_\_\_\_  
Date

**Do not use this form for consenting research participants unless a stamp appears here.**

*<<US sites only.>>*

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

**Appendix VI-B, Part 1: MASTER Sample Informed Consent Form for Participation in Component 2**  
*for women who can provide independent informed consent for study participation*

*[U.S. sites may NOT modify Part 1 of this consent form]*

**IMPAACT 2026**  
**Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum**

**Version 1.0, 22 January 2020**

***Introduction***

You and your baby are being asked to take part in the research study named above because you are pregnant and have received at least one injection with the long-acting drug **cabotegravir (CAB LA)** during your pregnancy as part of participation in a different research study.

This consent form gives information about this study. Please read it, or have it read to you, and ask any questions you may have. You may have as much time as needed to fully understand the study. We will ask you questions to see if we have explained the study clearly.

This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study, this informed consent form includes two parts. This part of the consent form includes general study information that applies to all study sites. The second part of the consent form includes information specific to the study site where you are being asked to enroll. Before making your decision, both parts of this form will be reviewed with you. You will have the opportunity to discuss any questions about this form and both of its parts with your site's study team.

***Key Information***

Here is a summary of important information about the study:

- The primary purpose of the study is to determine how much of the CAB LA that a woman received during pregnancy gets into her baby after delivery. Another purpose is to look at how safe the medicines are for mother and baby.
- If you choose to join the study, you will have your first study visit before you give birth and will have a study visit at delivery. Your baby will be in the study for up to five weeks after birth and will have at least three study visits.
- You will have blood drawn at each study visit after the first visit, to measure the amount of injectable cabotegravir in your blood, and your baby may have blood drawn at each visit too.
- You will be asked questions about your and your baby's health and you and your baby will have physical exams and routine blood tests.
- At select sites, women who breastfeed their baby will have breast milk collected and a couple extra study visits.
- There may be no direct benefit to you or your baby from being in the study. However, this study may help doctors learn information that will help future patients who receive cabotegravir injections.
- The most likely risk to you and your baby is from blood drawing- including pain, which is usually minor, and infection, which is rare.

- Your decision will have no effect on the medical care that you and your baby would normally receive from your clinic. Your access to services, and the benefits and rights you normally have, will not be affected.

More information is given in both parts of this form about the study, its risks and benefits. You should feel that you understand the study before deciding whether you and your baby will participate.

After you understand the study, and if you decide that you and your baby will join, you will be asked to sign or make your mark on this form. You will be offered a copy to keep. You do not give up any rights by signing this form.

### ***About the study***

This study is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network.

The study will measure the amounts of CAB LA in the blood of women who received it during pregnancy, and it will also measure the amount of CAB LA in the blood of their babies. At some sites, the study will also measure the amounts of CAB LA in the breast milk of women who choose to breastfeed. The study will include up to 28 mothers and their babies who received at least one injection of CAB LA during pregnancy, from Botswana, Brazil, India, Kenya, Malawi, South Africa, Tanzania, Thailand, Uganda, Zimbabwe, and the United States.

The United States National Institutes of Health are paying for this study.

#### **1. The study will measure the amounts of CAB in the blood of women who received it during pregnancy, and in the blood of their babies.**

You are already participating in another study of a new drug called CAB LA, which is an anti-HIV drug that may help to protect people from getting HIV and treat people who have HIV. Because it is a new drug, not much is known yet about the amount of CAB LA that gets from a mother's blood into her baby during pregnancy and how long the CAB LA is present in the infant. In this study, we will look at the levels of CAB LA in blood from your baby's umbilical cord and compare it to the amount of medicine in your blood at the time of delivery. We will also look to see how much of the CAB LA that you received during your pregnancy is present in the baby at birth and for a couple weeks after birth, and how safe these medicines are for you and your baby. At select study sites, for women who breastfeed their baby, we will also look to see how much of the CAB LA is in their breast milk, and how much gets from their breast milk into their baby's blood.

#### **2. Only pregnant women who are eligible can join the study.**

If you decide to join the study with your baby, we will first talk to you about the study and collect some information about you to find out if you are eligible. More information about this is given in section #4 below. If you are eligible, you can join the study. If you are not eligible, you cannot join the study.



**3. It is your decision whether or not you join the study.**

Deciding to join the study is voluntary (your choice). If you are eligible, you can choose if you want to join the study or not. You are free to join or not join. If you join, you must agree for your baby to join the study too. If you and your baby join, you can change your mind later and leave the study. Your decision will have no effect on the medical care that you and your baby would normally receive from your clinic. Your access to services, and the benefits and rights you normally have, will not be affected. If you decide to join, we will tell you any new information from this study or other studies that may affect your willingness to stay in the study. You are welcome to ask questions or request more information at any time.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. You can bring other people here to learn about the study with you.

***Finding out if You and Your Baby are Eligible for the Study***

**4. We will ask you questions, look at your medical records, and discuss the study with you.**

You will need to come to the clinic to make sure you are eligible for the study before you join. This may be done as part of your first study visit for this study or during your routine study visit for HPTN 084 or IMPAACT 2017, so a separate visit may not be required, but this must be done before you have your baby. To find out if you can join, we will talk to you about what you will have to do if you decide to join the study. We will collect some information from your medical records about you, your health, your pregnancy, and the medications that you take. We will tell you if you are or are not eligible for the study.

***Entering the study***

**5. If you are eligible, you will enter the study during your pregnancy before you have your baby.**

Women can only join the study when they are at least 24 weeks pregnant but have not yet delivered their baby. If you are eligible, we will tell you if it is the right time to enter the study.

**6. You will have one study visit when you enter the study before you give birth.**

You will have a study visit when you enter the study, before you give birth. At this visit, we will ask you about your health and do a physical exam. We will not draw any blood at this visit. This visit may also be done as part of a routine study visit for HPTN 084 or IMPAACT 2017, or it may be combined with the visit to find out if you are eligible for the study, so a separate visit may not be required.

***Being in the Study***

**7. You will have a study visit at the time of delivery.**

At or near the time of delivery, we will ask you questions about your health, do a physical exam, and do routine blood tests. Blood will also be drawn to measure the amount of CAB LA in your blood. A total of about 13 mL (a little under 3 teaspoons) of blood will be drawn. Right after your baby is born, a small amount of blood will also be drawn from the umbilical cord that is attached to the placenta after the cord is clamped and cut. This will be used to measure the amount of medicines that get into your baby's blood, but this blood comes from the placenta, and not from your baby.

You will be given the results of the routine blood tests. The tests to measure the amount of medicine levels in your blood and your baby's blood will be done later in the study, so you won't get results of these tests.

**8. Your baby will have study visits after birth.**

After your baby is born, your baby will be examined at least 3 times during the study: from birth to 3 days after birth, 5-9 days after birth, and 12-16 days after birth. During these visits, your baby will be weighed and measured and information about your baby's health will be recorded from his/her medical records. Your baby, if healthy enough, will have blood samples drawn to determine how much of the CAB LA that you received during pregnancy got into your baby's blood and how long it takes to get out. We will ask you about how you feed your baby. Your baby will have blood samples drawn at 3 times between birth and 3 days old, a fourth sample drawn between 5-9 days after birth and a fifth sample drawn at 12-16 days after birth. Less than 1 mL (less than ¼ teaspoon) of blood will be collected for each sample. The total amount of blood collected for these tests will be around 4 mL (less than 1 teaspoon). These blood tests will be done later in the study too, so you will not receive the results of these tests.

For select study sites, there will be additional study visits for you and your baby if you breastfeed your baby after birth. Part 2 of this form will provide details about these additional visits, if this clinic is one of the select study sites.

**9. Different tests will be done at different laboratories**

We will test some of your samples to check your health at our laboratory. Tests to determine the amount of medicine in your samples or your baby's samples will be done at other laboratories that have special tests for this. Samples for these special tests may be sent to laboratories in other countries.

**10. If you agree, some of your and your baby's blood will be used for genetic testing.**

If you agree, we will use some of your blood for genetic testing. Also, if you agree, we will collect one drop of blood for genetic testing of your baby. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people break down medicines differently and this can change the levels of the medicines in their bodies. If you agree, your and your child's blood would only be used to look at differences in specific genes that may affect the levels of some medicines. Testing of all of your or your child's genes, which is sometimes called whole genome sequencing, will not be done. You may decide that you do not want genetic testing for you or your baby. You may change your decision about having genetic testing at any time by contacting the study clinic. You can still join in this study even if you do not agree to genetic testing. This test will be done later in the study, so you will not receive the results of this test, and the results will not go into your medical records or have your name attached to them.

**Please write your initials or make your mark below to indicate your decision about genetic testing.**

<p><b>For YOUR optional genetic testing:</b></p> <p>_____ I agree to allow testing of my genes that can affect the levels of medicines in the body.</p> <p>_____ I do not agree to allow testing of my genes.</p> <p><b>For YOUR BABY'S optional genetic testing:</b></p> <p>_____ I agree to allow testing of my baby's genes that can affect the levels of medicines in the body.</p> <p>_____ I do not agree to allow testing of my baby's genes.</p>
--

**11. We may take you or your baby off of the study early.**

The study doctor may need to take you and your baby off the study early without your permission if:

- The study is stopped for any reason.
- You are/your baby is not able to attend the study visits as required by the study.
- We determine that staying in the study might harm you or your baby.

**12. Please tell us if you want to leave the study.**

You and your baby are free to leave the study at any time for any reason. The care that you receive at this clinic will not be affected, but it is important for us to know about your decision.

***Risks of the study***

Taking part in this study may involve some risks and discomfort.

**13. Risk from blood draws**

Blood drawing may cause fainting, lightheadedness or some discomfort. Other risks include bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or swelling of the surrounding skin may occur. There is also a small risk of a minor infection at the blood draw site. Blood drawing from your baby can also be done by heel stick. Heel stick may cause some discomfort, bleeding or bruising at the site of the heel stick. There is a small risk of infection at the site of the heel stick.

**14. There could be risks of disclosure of your information.**

We will make every effort to keep your and your baby's information private and confidential. Study records and specimens will be kept in secure, locked locations. All specimens and most records will be labeled only with a code number. However, your name will be written on some records.

Despite our best efforts to keep your information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stress or embarrassment.

### ***Benefits of the study***

**15. There may be no direct benefit to you or your baby from being in the study.**

If you take part in this study, there may be no direct benefit to you or your baby. You or your baby may benefit from having your or your baby's blood checked for safety effects. Information learned from this study may help others who receive CAB LA in the future.

### ***Other information about the study***

**16. There are no costs from being in the study.**

There is no cost for the study-related clinic visits, examinations, and laboratory tests in this study.

**17. Study records may be reviewed by study staff and groups that oversee the study.**

Groups that oversee the study include:

- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your or your baby's name or identify you or your baby personally.

A description of this study will be available on [ClinicalTrials.gov](http://ClinicalTrials.gov) as required by U.S. law. This website will not include information that can identify you or your baby. At most, the website will include a summary of the results. You can search this website at any time. If you want the results from this study, please tell the study staff.

Your or your baby's study information may be given to other authorities if required by law.

**18. What will happen with your data and specimens after the study.**

The samples collected from you and your baby will only be used for the testing described in this form. The samples will not be used for other research now or in the future. The samples will not be sold or used for commercial profit. For example, the samples will not be used to make a new product that could be sold.

Other information collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about HIV. Any future research done with the information from this study must be approved by the IMPAACT Network. If any future research is done, information about you or your baby may be used. Your or your baby's information will be labeled with a code number, and the only link between the code number and your name or your baby's name will be kept at this site. Your name or your baby's name will not be given to other researchers.

Data or information from the study may be shared with drug companies who have agreements with the IMPAACT Network and/or the U.S. NIH, or regulatory entities, but you or your baby will never be identified personally.

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

## Appendix VI-B Part 2: SITE-SPECIFIC Consent Information for Participation in Component 2

### PART 2: SITE-SPECIFIC CONSENT INFORMATION

**Site Name:**

**Study Title:** IMPAACT 2026: Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum, Version 1.0, 22 January 2020

JHM IRB Application Number: <<US sites only.>>

**Site Investigator of Record:**

**Site Principal Investigator Contact Information:**

**Emergency Contact:**

**Other Study Contact(s):**

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#### Introduction

This study is being done at multiple sites. This part of the consent form includes information about your site and is specific to participation at your site only. Before making your decision, both the site-specific information and general study information will be reviewed with you. You will have the opportunity to discuss any questions, including questions about this portion of the consent document, with your site's study team.

#### Site-Specific Study Procedures and Associated Risks

##### **Additional Study Visits for Women who Breastfeed their Baby**

<<Sites may choose to participate or not participate in breast milk transfer PK evaluations based on local standard of care breastfeeding practices. Sites must select one of the following two options of text based on this determination.>>

<<**Option 1:** For sites where breastfeeding is standard practice, include the following information.>>

This site is one of the select sites that will look at how much of the CAB LA gets into a mother's breast milk, and then into a baby's blood from drinking the breast milk, among women who breastfeed their baby after delivery. In addition to the visits that were described in Part 1 of this form, if you breastfeed after your baby is born, and if your baby is healthy, you will have three extra visits to look at how much of the CAB LA that you received during your pregnancy gets into your baby's blood through drinking breast milk. These extra visits would be within 5 weeks after giving birth.

You will have study visits with your baby at 5-9 days after birth, 12-16 days after birth, and 3-5 weeks after birth. At each of these visits, we will ask you about your health, do a physical exam, weigh and measure your baby, and record information about your baby's health from her/his medical records. We will draw one 2 mL blood sample from you (less than ½ teaspoon) at each visit. For your baby, we will draw less than 1 mL (less than ¼ teaspoon)

**Do not use this form for consenting research participants unless a stamp appears here.**

*<<US sites only.>>*

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

of blood at the visit at 3-5 weeks after birth. We will also collect a breast milk sample from you at the visits at 5-9 days after birth, 12-16 days after birth, and 3-5 weeks after birth.

We will use all of these samples to measure the amount of CAB LA your blood, in your baby's blood and in your breast milk. We will only collect these extra samples and have these extra visits if you are breastfeeding your baby at the time of the visit. If you do not breastfeed your baby or are not breastfeeding your baby at the time of the visit, we will not do these extra visits or collect the extra samples for breast milk testing. These tests will be done later in the study, so you will not receive the results.

Each of these visits for you and your baby will last about *<<sites add local information about time for study visits>>*.

*<< Option 2: For sites where breastfeeding is NOT standard practice, include the following information.>>*

This site is not one of the select sites that will look at the amount of CAB LA in breast milk that gets into a baby's blood. All of the study visits you and your baby will have are described in Part 1 of this form.

#### **Costs to Study Participants:**

*<<Brief description of costs to participants. Only include if different than costs as described in the main consent document. >>*

*Example:* Any medical costs for your treatment outside this study will be charged to you or your health insurance company. This study will not cover any cost related to your pregnancy and delivery or care of your baby.

#### **Payment for Study Participation:**

*<<Brief description of payments and/or reimbursements.>>*

#### **Compensation for Research-Related Injury:**

Your health is important to us. We will make every effort to protect your and your baby's well-being and minimize risks.

*<<Add any locally-required language for research-related injury and contact information outlining who subjects should call in the event of any research-related injuries. Information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement about no compensation through the US NIH is mandatory for all sites and may not be deleted.>>*

If you are/your baby is injured as a result of being in this study, you/your baby will be given immediate treatment for your/your baby's injuries. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation through the United States National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

#### **Certificate of Confidentiality**

*<<U.S. SITES only MUST include, sites outside of the U.S. MUST delete Certificate of Confidentiality section:>>*

**Do not use this form for consenting research participants unless a stamp appears here.**

*<<US sites only.>>*

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify you or your baby, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you or your baby. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

### **Contact Information:**

**If you have questions, concerns, or problems at any time, use these contacts.**

- If you have questions about the study:  
*<< insert name and telephone number of investigator or other study staff >>*
- If you or your baby have any health or other problems that may be related to study participation:  
*<< insert name and telephone number of investigator or other study staff >>*
- If you want to leave the study:  
*<< insert name and telephone number of investigator or other study staff >>*
- *<< Non-U.S. sites should modify the following as appropriate.>>* This study has been reviewed by an Institutional Review Board (IRB), a group of people that reviews human research studies. The IRB protects the rights and welfare of the people taking part in those studies. The IRB can help you if you have questions about your or your child's rights as a research participant or if you have other questions, concerns or complaints about this research study. If you have questions about your or your baby's rights as research participants or concerns about how you are/your baby is being treated in the study:
  - For this multi-site study, Johns Hopkins has agreed to serve as the single IRB (sIRB) providing oversight for all sites in the U.S. You may contact the Johns Hopkins IRB at **410-502-2092** or **jhmeirb@jhmi.edu** with your questions or concerns.
  - You may also contact the [*site specific IRB contact information*] with your questions or concerns. *<< If your site wishes to include local IRB contact information, please include this here. If this is not required, please delete this section. >>*

### **Additional information about your local site:**

*<<Please insert any additional required language for your site, as applicable for this study. Examples may include*

- *Local regulatory authorities that may review study records (if different from those listed in Part 1 #17)*
- *Local language regarding state law requirements for reporting of communicable diseases or other mandated reporting requirements.*
- *Locally required language for any specific research procedures, e.g. commercialization of cell lines.*
- *Local conflict of interest disclosures*

### **How will your privacy be maintained and how will the confidentiality of your data be protected?**

*<< Insert locally-required HIPAA authorization language. The following language has already been approved by the JHM IRB. Please consider whether this language may be used at your site:*

- *If this language is acceptable, it may remain in this section.*



**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

- *If this language is not acceptable, and locally-approved HIPAA authorization language is required, please delete the language and replace it with your own language.*
- *Alternatively, if your site requires use of a separate HIPAA authorization, please delete this section and include the following sentence: “[Add site name] requires that you sign a separate authorization form related to the use of your protected health information for this research study. This is required for participation in this study.” >>*

### **HIPAA Authorization for Disclosure of Protected Health Information**

#### **What information is being collected, used, or shared?**

To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

#### **Who will see, use or share the information?**

The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at << *insert site name* >>, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of << *insert site name* >>. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

#### **Do you have to sign this Authorization?**

You do not have to sign this Authorization, but if you do not, you may not join the study.

#### **How long will your information be used or shared?**

Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

#### **What if you change your mind?**

You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

**Signature Lines:**

<<US sites: If your site wishes to include site-specific signature lines, please include them here. If your site does not have site-specific signature requirements, the JHM IRB signature lines will be added in this section.  
Non-US sites: If your site wishes to include site-specific signature lines, please include them here. If your site does not have site-specific signature requirements, please use the template lines provided below. >>

**If you agree to participate in this study, please sign or make your mark below.**

\_\_\_\_\_  
Name of Participant  
(print)

\_\_\_\_\_  
Signature of Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Study Staff Conducting  
Consent Process Name (print)

\_\_\_\_\_  
Signature of Study Staff

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Witness  
(as appropriate; print)

\_\_\_\_\_  
Signature of Witness

\_\_\_\_\_  
Date

## Appendix VI-C, Part 1: MASTER Sample Informed Consent Form for Participation in Component 3

*[U.S. sites may NOT modify Part 1]*

### PART 1: MASTER INFORMED CONSENT FORM

#### IMPAACT 2026

#### Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum

Version 1.0, 22 January 2020

##### **Introduction**

You and your baby are being asked to take part in the research study named above because you are pregnant and taking one or more of the following HIV medicines in pregnancy: **dolutegravir, atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir**; along with at least two of the following TB medicines: **isoniazid, rifampin, rifabutin, ethambutol, pyrazinamide, and/or moxifloxacin**.

This consent form gives information about the study. Please read it, or have it read to you, and ask any questions you may have. You may have as much time as you need to fully understand the study. We will ask you questions to see if we have explained the study clearly.

This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study, this informed consent form includes two parts. This part of the consent form includes general study information that applies to all study sites. The second part of the consent form includes information specific to the study site where you are being asked to enroll. Before making your decision, both parts of this form will be reviewed with you. You will have the opportunity to discuss any questions about this form and both of its parts with your site's study team.

##### **Key Information**

Here is a summary of important information about the study:

- The primary purpose of the study is to determine how much HIV and TB medicine is in a woman's blood during pregnancy. Another purpose is to look at how much HIV and TB medicines gets into her baby after delivery, and how safe the medicines are for mother and baby.
- If you choose to join the study, you will have your first visit during the second or third trimester of your pregnancy and will stay in the study for at least 3 months after you deliver. You will have one or two study visits while you are pregnant, a study visit at delivery and at least one study visit after your baby is born. Your baby will be in the study for about 6 months after birth. Your baby will have at least three study visits.
- You will continue to receive the HIV and TB treatment medicines given by your health care provider.
- You will have blood drawn at each study visit to measure the amount of HIV and TB medicine in your blood, and your baby may have blood drawn at each visit too. You will be asked questions about your and your baby's health and you and your baby will have physical exams and routine blood tests. You will also have blood drawn to check the amount of HIV in your blood.
- At select sites, women who breastfeed their baby will have breast milk collected and a couple extra study visits. There may be no direct benefit to you or your baby from being in the study. However,

this study may help doctors learn information that will help in the treatment of future patients with HIV and TB.

- The most likely risk to you and your baby is from blood drawing- including pain, which is usually minor, and infection, which is rare.
- Your decision will have no effect on the medical care that you and your baby would normally receive from your clinic. Your access to services, and the benefits and rights you normally have, will not be affected.

More information is given in both parts of this form about the study, its risks and benefits. You should feel that you understand the study before deciding whether you and your baby will participate.

After you understand the study, if you decide that you and your baby will join the study, you will be asked to sign or make your mark on this form. You will be offered a copy to keep. You do not give up any rights by signing this form.

### ***About the study***

This study is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT).

The study will measure the amounts of different HIV medicines and TB medicines in the blood of pregnant women and their babies. At some sites, the study will also measure the amounts of HIV and TB medicines in the breast milk of women who choose to breastfeed after giving birth. The study will include up to 28 mothers and their babies for each HIV medicine or combination of medicines that we are looking at, from Botswana, Brazil, India, Kenya, Malawi, South Africa, Tanzania, Thailand, Uganda, Zimbabwe, and the United States. You and your baby will be in the study through your pregnancy and for up to 24 weeks after your baby is born.

The United States National Institutes of Health are paying for this study.

#### **1. The study will measure the amounts of HIV and TB medicines in the blood of pregnant women and their babies.**

The amount of tuberculosis medicines needed during pregnancy to treat tuberculosis infection has not been studied. When tuberculosis medicines are taken together with HIV medicines, the TB medicines may decrease the amount of the HIV medicines in the blood, so that the correct doses of the HIV medicines needed to protect your baby from HIV infection while being safe for you and your baby are not known. In this study, we will measure levels of certain TB and HIV medicines in you and in other HIV-infected pregnant women who have TB.

We will compare the levels of tuberculosis medicines found in this study to those in HIV-uninfected pregnant women who have TB and are on the same tuberculosis medicines. We will also compare the levels of HIV medicines to those in HIV-infected, non-pregnant adults who do not have tuberculosis but are on the same HIV medicines.

We will also be looking at the levels of medicines found in blood from your baby's umbilical cord and comparing it to the amount of medicine in your blood at the time of delivery. We will also look to see how much of the TB and HIV medicines you took while you were pregnant are present in your baby's blood at birth and for a few days after birth, and how safe these medicines are for you and your baby. At select study sites, for women who breastfeed their baby, we will also look to see how much of the HIV and TB medicines are in their breast milk, and how much gets from their breast milk into their baby's blood.

**2. Only pregnant women who are eligible can join this study.**

If you decide to join the study with your baby, we will first talk to you about the study and collect some information about you to find out if you are eligible. More information about this is given in #4 below. If you are eligible, you can join the study. If you are not eligible, you cannot join the study.

**3. It is your decision whether or not you join the study.**

Deciding to join the study is voluntary (your choice). If you are eligible, you can choose if you want to join the study or not. You are free to join or not join. If you join, you must agree for your baby to join the study too. If you and your baby join, you can change your mind later and leave the study. Your decision will have no effect on the medical care that you and your baby would normally receive from your clinic. Your access to services, and the benefits and rights you normally have, will not be affected. If you decide to join, we will tell you any new information from this study or other studies that may affect your willingness to stay in the study. You are welcome to ask questions or request more information at any time.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. You can bring other people here to learn about the study with you.

***Finding out if You and Your Baby are Eligible for the Study***

**4. We will ask you questions, look at your medical records, and discuss the study with you.**

You will need to come to the clinic to make sure you are eligible for the study before you join. This may be done as part of your first study visit or a routine care visit, so a separate visit may not be required. To find out if you can join, we will talk to you about what you will have to do if you decide to join the study. We will collect some information from your medical records about you, your health, your pregnancy, and the medications that you take. We may test your blood for HIV to confirm your status. If we test your blood for HIV, we will give you the results. We will tell you if you are or are not eligible for the study.

***Entering the study***

**5. If you are eligible, you will enter the study during your second or third trimester.**

Women may only join the study when they are 20-26 weeks pregnant or 30-37 weeks pregnant. If you are eligible, we will tell you when it is the right time to enter the study. You will also need to be on your HIV and TB medicines for at least 2 weeks before your first study visit.

***Being in the study***

**6. You will continue to take your HIV and TB medicines.**

If you join the study, you will continue to receive and take your HIV and TB medicines as you normally would. No medicines are supplied by this study. It will be important for you to continue with all of your regular HIV care even if you join the study.

**7. You will have up to two study visits during your pregnancy and at least one study visit after giving birth.**

If you enroll in the study during your second trimester, you will have a study visit when you are 20-26 weeks pregnant, a study visit when you are 30-37 weeks pregnant, and a study visit 2-8 weeks after you give birth. If you

enroll during your third trimester, you will only have one visit during your pregnancy when you are 30-37 weeks pregnant, as well as the visit 2-8 weeks after you give birth.

At each visit, we will ask you about your health, do a physical exam, and do routine blood tests. We will also draw blood to check how well your body is able to fight infection and to check the amount of HIV in your blood. The total amount of blood drawn for these tests is about 13 mL (2 ½ teaspoons). You will be given the results of these tests. At each visit you will be asked about taking your medicines.

At each visit, repeat blood samples will also be drawn to measure the amount of HIV and TB medicines in your blood. A small plastic catheter (soft tube) will be placed in a vein in your arm during this visit, so that blood can be drawn multiple times, without having to stick you with a needle several times. The tube may stay in place until all of the blood samples are drawn. Depending on the medicine(s) you are taking and the time you usually take them, 7 blood samples over 12 hours or 8 blood samples over 24 hours will be collected. We will explain to you the blood sampling schedule that will be used for you. Each time, we will draw about 4 mL (less than 1 teaspoon) of blood, for a total of between 31-35 mL (about 7 teaspoons). These repeat blood samples will only be drawn at a visit if you are still taking the TB and HIV medicines.

For three days before your visit, you must be sure to take your medicines at the same time each day, but you must **not** take your medicine(s) on the day you come to the clinic for your study visit. This is very important. We will help you remember this before the visit.

When you come to the visit, we will place a small catheter (soft tube) into your arm and draw your first blood sample, then you will take your HIV medicine(s), and then we will draw the rest of your blood samples over 12 or 24 hours from the same catheter so we can avoid multiple pokes during the day. You will be asked to tell us the times of your previous two doses of medicines and to describe the time and amount of your previous two meals. Before these repeat blood samples are drawn, the study staff will review with you any dietary recommendations related to the HIV medicines you are taking.

If you have blood samples collected over 24 hours, you may be permitted to remain in the clinic overnight, or you may be able to leave the clinic after your last blood draw before the 24 hour blood draw, in which case you must return for the 24 hour blood draw at the time the clinic tells you to return. Part 2 of this form provides more information about what will happen for you at this clinic.

While you are pregnant, your HIV medicine levels will be reported back to you and your doctor as soon as possible once they have been determined. If any of these levels are low compared to those in non-pregnant adults, you and your doctor will be told. You may decide, in consultation with your doctor, to adjust the dose of the HIV medicine(s). If you and your doctor choose to change your dose of HIV medicine(s), you may choose to have your blood checked for medication levels on your new dose of medication. After you give birth, your HIV medicine levels testing will be done in batches later in the study, so you and your doctor won't get results of these tests. The TB medicine levels and testing will be done in batches later in the study, so you and your doctor won't get results of these tests at any time.

In addition to these visits, there will also be a study visit at the time of delivery (see #8 below) and visits for your baby (see #9 below). For select study sites, there will be additional study visits for you and your baby if you breastfeed your baby after birth. Part 2 of this form will provide details about these additional visits, if this clinic is one of the select study sites.

#### **8. You will have a study visit at the time of delivery.**

At or near the time of delivery, we will ask you questions about your health, do a physical exam, and do routine blood tests. Blood will also be drawn to check how well your body is able to fight infection, to check the amount

of HIV in your blood, and to measure the amount of HIV and TB medicines in your blood. About 18 mL of (3 ½ teaspoons) of blood will be drawn. After your baby is born, a small amount of blood will also be drawn from the umbilical cord that is attached to the placenta after the cord is clamped and cut. This will be used to measure the amount of medicines that get into your baby's blood, but this blood comes from the placenta, and not from your baby. You will be given the results of all tests, except the tests to measure the amount of HIV medicines in your blood and the blood from your umbilical cord.

**9. Your baby will have study visits after birth.**

After your baby is born, your baby will be examined 3 times during the study: from birth to 3 days after birth, 5-9 days after birth, and at 4-6 months of age. During these visits, your baby will be weighed and measured and information about your baby's health will be recorded from his/her medical records. If your baby is healthy enough, we will also collect some blood samples to determine how much of the HIV and TB medication that you took during pregnancy got into your baby and how long after birth they are present in your baby's blood. We will ask you about how you feed your baby. Your baby will have blood samples drawn at 3 times between birth and 3 days old, and a fourth sample drawn between 5 and 9 days after birth. About 1 mL (less than ¼ teaspoon) of blood will be collected for each sample. The total amount of blood collected for these tests will be around 4 mL (less than 1 teaspoon). These tests will be done later so you will not receive the results of these tests.

Each of your baby's study visits will last about 30 minutes to 1 hour.

For select sites, there will also be an additional examination if you breastfeed your baby. If these additional examinations will happen here at this site, this will be described more in Part 2 of this form.

**10. Different tests will be done at different laboratories**

We will test some of your samples to check your health at our laboratory. Tests to determine the amount of medicine in your samples or your baby's samples will be done at other laboratories that have special tests for this. Samples for these special tests may be sent to laboratories in other countries.

**11. If you agree, some of your and your baby's blood will be used for genetic testing**

If you agree, we will use some of your blood for genetic testing. Also, if you agree, we will collect one drop of blood for genetic testing of your baby. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people break down medicines differently and this can change the levels of the medicines in their bodies. If you agree, your and your child's blood would only be used to look at differences in specific genes that may affect the levels of some medicines. Testing of all of your or your child's genes, which is sometimes called whole genome sequencing, will not be done. You may decide that you do not want genetic testing for you or your baby. You may change your decision about having genetic testing at any time by contacting the study clinic. You can still join in this study even if you do not agree to genetic testing. This test will be done later in the study, so you will not receive the results of this test, and the results will not go into your medical records or have your name attached to them.

**Please write your initials or make your mark below to indicate your decision about genetic testing.**

**For YOUR optional genetic testing:**

\_\_\_\_\_ I agree to allow testing of my genes that can affect the levels of medicines in the body.

\_\_\_\_\_ I do not agree to allow testing of my genes.

**For YOUR BABY'S optional genetic testing:**

\_\_\_\_\_ I agree to allow testing of my baby's genes that can affect the levels of medicines in the body.

\_\_\_\_\_ I do not agree to allow testing of my baby's genes.

**12. We may take you or your baby off of the study early.**

The study doctor may need to take you and your baby off the study early without your permission if:

- The study is stopped for any reason.
- You are/your baby is not able to attend the study visits as required by the study.
- We determine that staying in the study might harm you or your baby.

If you must stop taking the HIV and/or TB medicine(s) before the study is over, we may ask you to continue to be part of the study and return for the scheduled study visits and some of the procedures. If you stop the study HIV and/or TB medicines, we also may ask that your baby stay in the study and complete the scheduled study visits and some of the procedures as described in #9 above.

**13. Please tell us if you want to leave the study.**

You and your baby are free to leave the study at any time for any reason. The care that you receive at this clinic will not be affected, but it is important for us to know about your decision.

***Risks of the study***

Taking part in this study may involve some risks and discomfort.

**14. Risk from blood draws**

Blood drawing may cause fainting, lightheadedness or some discomfort. Other risks include bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or swelling of the surrounding skin may occur. There is also a small risk of a minor infection at the blood draw site. Blood drawing from your baby can also be done by heel stick. Heel stick may cause some discomfort, bleeding or bruising at the site of the heel stick. There is a small risk of infection at the site of the heel stick.

**15. There could be risks of disclosure of your information.**

We will make every effort to keep your and your baby's information private and confidential. Study records and specimens will be kept in secure, locked locations. All specimens and most records will be labeled only with a code number. However, your name will be written on some records.



Despite our best efforts to keep your information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stress or embarrassment.

***Benefits of the study***

**16. There may be no direct benefit to you or your baby from being in the study.**

If you take part in this study, there may be no direct benefit to you or your baby. You may benefit from having the levels of HIV medicine(s) in your blood measured and having your blood checked for safety effects. Information learned from this study may help others who have HIV and tuberculosis.

***Other information about the study***

**17. There are no costs from being in the study.**

There is no cost for the study-related clinic visits, examinations, and laboratory tests in this study.

**18. Study records may be reviewed by study staff and groups that oversee the study.**

Groups that oversee the study include:

- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your or your baby's name or identify you or your baby personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you or your baby. At most, the website will include a summary of the results. You can search this website at any time. If you want the results from this study, please tell the study staff.

Your or your baby's study information may be given to other authorities if required by law.

**19. What will happen with your data and specimens after the study.**

The samples collected from you and your baby will only be used for the testing described in this form. The samples will not be used for other research now or in the future. The samples will not be sold or used for commercial profit. For example, the samples will not be used to make a new product that could be sold.

Other information collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about HIV. Any future research done with the information from this study must be approved by the IMPAACT Network. If any future research is done, information about you or your baby may be used. Your or your baby's information will be labeled with a code

number, and the only link between the code number and your name or your baby's name will be kept at this site. Your name or your baby's name will not be given to other researchers.

Data or information from the study may be shared with drug companies who have agreements with the IMPAACT Network and/or the U.S. NIH, or regulatory entities, but you or your baby will never be identified personally.

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

## Appendix VI-C Part 2: SITE-SPECIFIC Consent Information for Participation in Component 3

### PART 2: SITE-SPECIFIC CONSENT INFORMATION

**Site Name:**

**Study Title:** IMPAACT 2026: Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum, Version 1.0, 22 January 2020

JHM IRB Application Number: <<US sites only.>>

**Site Investigator of Record:**

**Site Principal Investigator Contact Information:**

**Emergency Contact:**

**Other Study Contact(s):**

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#### Introduction

This study is being done at multiple sites. This part of the consent form includes information about your site and is specific to participation at your site only. Before making your decision, both the site-specific information and general study information will be reviewed with you. You will have the opportunity to discuss any questions, including questions about this portion of the consent document, with your site's study team.

#### Site-Specific Study Procedures and Associated Risks

**Procedures for Repeat Blood Samples**

As described in Part 1 #7 of this form, we will collect repeat blood samples from you several times over 24 hours at up to two visits during your pregnancy and one visit after you give birth.

<<Sites should select one of the following descriptions of procedures for intensive PK blood samples collected over 24 hours, to clarify the information provided in #7 of Part 1 and to specify what will happen for participants at your site. Sites may modify the description if necessary, to further make site specific or provide any additional details relevant to the local context.>>

*Example 1:* For these visits, you will need to stay throughout the day and overnight at the clinic or hospital for up to 24 hours.

*Example 2:* For these visits, you will stay in the clinic or hospital through the second-to-last blood draw (the blood draw before your final blood draw at 24 hours), but you can go home after that and return to the clinic the next day for the final 24-hour blood draw. It is also possible to have room accommodations made within walking distance to the clinic or hospital for this visit.

**Additional Study Visits at Select Sites for Women who Breastfeed their Baby**

<<Breast milk transfer PK evaluations may be performed at sites participating in Arms 3.2 and/or 3.3. For these arms, sites may choose to participate or not participate in these breast milk transfer evaluations based on local

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Lead Study Investigator:

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Site Specific Consent Information Approval Date:

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*standard of care breastfeeding practices. Sites should select one of the following two options of text based on this determination.>>*

*<<Option 1: For sites where breastfeeding is standard practice, include the following text, modify as appropriate based on planned study arm participation, and deleted Option 2.>>*

*<<If enrolling participants to Arm 3.2 and/or 3.3, include the following information.>>*

For women taking **atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir**, this site is one of the select sites that will look at how much of the HIV medicines get into a mother's breast milk, and then into a baby's blood from drinking the breast milk, among women who breastfeed their baby after delivery. If you breastfeed your baby after delivery, and if your baby is healthy, you will have additional study visits with your baby at 5-9 days after birth and 4-6 months after birth, and your baby will have an additional visit with you at 2-8 weeks after birth. At each of these visits, we will ask you about your health, do a physical exam, weigh and measure your baby, and record information about your baby's health from her/his medical records. If we are not already drawing blood to measure the amount of HIV and TB medicine in your or your baby's blood as part of the study visit, we will draw a blood sample from you and your baby:

- For you, at 5-9 days after birth and 4-6 months after birth, we will draw one 4 mL sample of blood (less than ½ teaspoon) at each visit.
- For your baby, about 1 mL (less than ¼ teaspoon) of blood will be drawn at 2-8 weeks after birth and at 4-6 months after birth.
- We will also collect a breast milk sample from you at the visits at 5-9 days after birth, 2-8 weeks after birth, and 4-6 months after birth.

From all of these samples, we will measure the amount of HIV and TB medicines in your blood, in your baby's blood, and in your breast milk, to determine how much of the medicines that you take get into your baby through drinking breast milk. We will only collect these extra samples and have these extra visits if you are breastfeeding your baby at the time of the visit. If you do not breastfeed your baby or are no longer breastfeeding your baby at the time of the visit, we will not do these extra visits or collect the extra samples for breast milk testing. These tests will be done later in the study, so you will not receive the results.

For three days before your visit, you must be sure to take your medicines at the same time each day. This is very important. We will help you remember this before the visit.

Each of the extra visits for you or your baby will last about <<sites add local information about time for study visits>>.

*<< If enrolling participants to Arm 3.1, including the following information>>.*

For women taking **dolutegravir**, we will not look at the amount of dolutegravir in breast milk that gets into a baby's blood. You and your baby will not have these additional visits. All of the study visits you and your baby will have are described in Part 1 of this form.

*<< Option 2: For sites where breastfeeding is **NOT** standard practice, include the following information and delete all Option 1 text, regardless of planned study arm participation.>>.*

This site is not one of the select sites that will look at the amount of HIV medicines in breast milk that get into a baby's blood. All of the study visits you and your baby will have are described in Part 1 of this form.

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

### **Costs to Study Participants:**

<<Brief description of costs to participants. Only include if different than costs as described in the main consent document. >>

*Example:* Any medical costs for your treatment outside this study, including your prescribed medicines for HIV, will be charged to you or your health insurance company. This study will not cover any cost related to your pregnancy and delivery or care of your baby.

### **Payment for Study Participation:**

<<Brief description of payments and/or reimbursements.>>

### **Compensation for Research-Related Injury:**

Your health is important to us. We will make every effort to protect your and your baby's well-being and minimize risks.

<<Add any locally-required language for research-related injury and contact information outlining who subjects should call in the event of any research-related injuries. Information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement about no compensation through the US NIH is mandatory for all sites and may not be deleted.>>

If you are/your baby is injured as a result of being in this study, you/your baby will be given immediate treatment for your/your baby's injuries. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation through the United States National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

### **Certificate of Confidentiality**

<<U.S. SITES only MUST include, sites outside of the U.S. MUST delete Certificate of Confidentiality section:>>

To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify you or your baby, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you or your baby. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

### **Contact Information:**

**If you have questions, concerns, or problems at any time, use these contacts.**

- If you have questions about the study:  
<< insert name and telephone number of investigator or other study staff >>
- If you or your baby have any health or other problems that may be related to study participation:  
<< insert name and telephone number of investigator or other study staff >>
- If you want to leave the study:  
<< insert name and telephone number of investigator or other study staff >>

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

- << *Non-U.S. sites should modify the following as appropriate.* >> This study has been reviewed by an Institutional Review Board (IRB), a group of people that reviews human research studies. The IRB protects the rights and welfare of the people taking part in those studies. The IRB can help you if you have questions about your or your child's rights as a research participant or if you have other questions, concerns or complaints about this research study. If you have questions about your or your baby's rights as research participants or concerns about how you are/your baby is being treated in the study:
  - For this multi-site study, Johns Hopkins has agreed to serve as the single IRB (sIRB) providing oversight for all sites in the U.S. You may contact the Johns Hopkins IRB at **410-502-2092** or **jhmeirb@jhmi.edu** with your questions or concerns.
  - You may also contact the [site specific IRB contact information] with your questions or concerns. <<If your site wishes to include local IRB contact information, please include this here. If this is not required, please delete this section. >>

#### **Additional information about your local site:**

<<Please insert any additional required language for your site, as applicable for this study. Examples may include

- *Local regulatory authorities that may review study records (in addition to those listed in Part 1 #18)*
- *Local language regarding state law requirements for reporting of communicable diseases or other mandated reporting requirements*
- *Locally required language for any specific research procedures, e.g. commercialization of cell lines*
- *Local conflict of interest disclosures*

#### **How will your privacy be maintained and how will the confidentiality of your data be protected?**

<< Insert locally-required HIPAA authorization language. The following language has already been approved by the JHM IRB. Please consider whether this language may be used at your site:

- *If this language is acceptable, it may remain in this section.*
- *If this language is not acceptable, and locally-approved HIPAA authorization language is required, please delete the language and replace it with your own language.*
- *Alternatively, if your site requires use of a separate HIPAA authorization, please delete this section and include the following sentence: "[Add site name] requires that you sign a separate authorization form related to the use of your protected health information for this research study. This is required for participation in this study." >>*

#### **HIPAA Authorization for Disclosure of Protected Health Information**

##### **What information is being collected, used, or shared?**

To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

##### **Who will see, use or share the information?**

The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at << insert site name >>, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

share your information with others outside of << insert site name >>. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

**Do you have to sign this Authorization?**

You do not have to sign this Authorization, but if you do not, you may not join the study.

**How long will your information be used or shared?**

Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

**What if you change your mind?**

You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

**Signature Lines:**

*<<US sites: If your site wishes to include site-specific signature lines, please include them here. If your site does not have site-specific signature requirements, the JHM IRB signature lines will be added in this section.*

*Non-US sites: If your site wishes to include site-specific signature lines, please include them here. If your site does not have site-specific signature requirements, please use the template lines provided below. >>*

**If you agree to participate in this study, please sign or make your mark below.**

\_\_\_\_\_  
Name of Participant  
(print)

\_\_\_\_\_  
Signature of Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Study Staff Conducting  
Consent Process Name (print)

\_\_\_\_\_  
Signature of Study Staff

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Witness  
(as appropriate; print)

\_\_\_\_\_  
Signature of Witness

\_\_\_\_\_  
Date

## Appendix VI-D Part 1: MASTER Sample Informed Consent Form for Participation in Component 4

*[U.S. sites may NOT modify Part 1]*

### IMPAACT 2026 Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum

Version 1.0, 22 January 2020

#### ***Introduction***

You and your baby are being asked to take part in the research study named above because you are pregnant and are taking one or more of the following tuberculosis (TB) medicines during your pregnancy: **moxifloxacin, levofloxacin, clofazimine, linezolid, bedaquiline, and/or delamanid**. Women in this study may also be living with HIV and taking HIV medications in combination with at least one of these TB medicines; specifically, the HIV medications: efavirenz, lopinavir, atazanavir, darunavir, dolutegravir, nevirapine, and/or raltegravir.

This consent form gives information about the study. Please read it, or have it read to you, and ask any questions you may have. You may have as much time as needed to fully understand the study. We will ask you questions to see if we have explained the study clearly.

This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study, this informed consent form includes two parts. Part 1 of the consent form includes general study information that applies to all study sites. Part 2 of the consent form includes information specific to the study site where you are being asked to enroll. Before making your decision, both parts of this form will be reviewed with you. You will have the opportunity to discuss any questions about this form and both of its parts with your site's study team.

#### ***Key Information***

Here is a summary of important information about the study:

- The primary purpose of the study is to determine how much TB medicine is in a woman's blood during pregnancy. Another purpose is to look at how much TB medicine gets into her baby after delivery, and how safe the medicines are for mother and baby.
- For women who are living with HIV and taking certain HIV medications in along with the TB medicines, a purpose of the study is also to look at how much HIV medicine is in a woman's blood during pregnancy, how much gets into her baby after delivery, and how safe the medicines are for mother and baby.
- If you choose to join the study, you will have your first visit during the second or third trimester of your pregnancy and will stay in the study for at least 3 months after you deliver. You will have one or two study visits while you are pregnant, a study visit at delivery and at least one study visit after your baby is born. Your baby will be in the study for about 6 months after birth. Your baby will have at least three study visits.
- You will continue to receive the TB treatment medicines given by your health care provider.
- You will have blood drawn at each study visit to measure the amount of TB medicines in your blood, and your baby may have blood drawn at each visit too.



- You will be asked questions about your and your baby's health and you and your baby will have physical exams and routine blood tests.
- At select sites, women who breastfeed their baby will have breast milk collected and a couple extra study visits.
- There may be no direct benefit to you or your baby from being in the study. However, this study may help doctors learn information that will help in the treatment of future patients with TB.
- The most likely risk to you and your baby is from blood drawing- including pain, which is usually minor, and infection, which is rare.
- Your decision will have no effect on the medical care that you and your baby would normally receive from your clinic. Your access to services, and the benefits and rights you normally have, will not be affected.

More information is given in both parts of this form about the study, its risks and benefits. You should feel that you understand the study before deciding whether you and your baby will participate.

After you understand the study, and if you decide that you and your baby will join the study, you will be asked to sign or make your mark on this form. You will be offered a copy to keep. You do not give up any rights by signing this form.

### ***About the study***

This study is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT).

The study will measure the amounts of different TB medicines in the blood of pregnant HIV-uninfected women and women who are living with HIV, and their babies. At some sites, the study will also measure the amounts of TB medicines in the breast milk of women who choose to breastfeed after giving birth. The study will include up to 28 mothers and their babies who are taking at least one of the TB medicines that we are studying, from Botswana, Brazil, India, Kenya, Malawi, South Africa, Tanzania, Thailand, Uganda, Zimbabwe, and the United States. You and your baby will be in the study through your pregnancy and for up to 24 weeks after your baby is born.

The United States National Institutes of Health are paying for this study.

#### **1. The study will measure the amounts of TB medicines in the blood of pregnant women and their babies.**

The amount of TB medicines needed during pregnancy to treat TB infection has not been studied. In this study, we will measure levels of TB medicines in pregnant women who are living with HIV and HIV-uninfected women before and after delivery. The amount of TB medicine found in blood from your baby's umbilical cord will be compared to the amount of medicine in your blood at the time of delivery. We will also look to see how much of the TB medicines you took while you were pregnant are present in your baby's blood at birth and for a few days after birth, and how safe these medicines are for you and your baby. At select study sites, for women who breastfeed their baby, we will also look to see how much of the TB medicines are in their breast milk, and how much gets from their breast milk into their baby's blood.

When TB medicines are taken together with HIV medicines, the TB medicines may decrease the amount of the HIV medicines in the blood, so that the correct doses of the HIV medicines needed to protect your baby from HIV infection while being safe for you and your baby are not known for all HIV medicines. If you are also taking certain HIV medicines, we will measure the amounts of HIV medicines in your and your baby's blood at all of these times as well.

**2. Only pregnant women who are eligible can join the study.**

If you decide to join the study with your baby, we will first talk to you about the study and collect some information about you to find out if you are eligible. More information about this is given in section #4 below. If you are eligible, you can join the study. If you are not eligible, you cannot join the study.

**3. It is your decision whether or not you join the study.**

Deciding to join the study is voluntary (your choice). If you are eligible, you can choose if you want to join the study or not. You are free to join or not join. If you join, you must agree for your baby to join the study too. If you and your baby join, you can change your mind later and leave the study. Your decision will have no effect on the medical care that you and your baby would normally receive from your clinic. Your access to services, and the benefits and rights you normally have, will not be affected. If you decide to join, we will tell you any new information from this study or other studies that may affect your willingness to stay in the study. You are welcome to ask questions or request more information at any time.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. You can bring other people here to learn about the study with you.

***Finding out if You and Your Baby are Eligible for the Study***

**4. We will ask you questions, look at your medical records, and discuss the study with you.**

You will need to come to the clinic to make sure you are eligible for the study before you join. This may be done as part of your first study visit or during a routine care visit, so a separate visit may not be required. To find out if you can join, we will talk to you about what you will have to do if you decide to join the study. We will collect some information from your medical records about you, your health, your pregnancy, and the medications that you take. We may test your blood for HIV to confirm your status. If we test your blood for HIV, we will give you the results. We will tell you if you are or are not eligible for the study.

***Entering the study***

**5. If you are eligible, you will enter the study during your second or third trimester.**

Women may only join the study when they are 20-26 weeks pregnant or 30-37 weeks pregnant. If you are eligible, we will tell you when it is the right time to enter the study. You will also need to be on your TB medicines for at least 2 weeks before your first study visit.

***Being in the study***

**6. You will continue to take your TB medicines.**

If you join the study, you will continue to receive and take your TB medicines as you normally would. No medicines are supplied by this study. It will be important for you to continue with all of your regular HIV care even if you join the study.

**7. You will have up to two study visits during your pregnancy and at least one study visit after giving birth.**

If you enroll in the study during your second trimester, you will have a study visit when you are 20-26 weeks pregnant, a study visit when you are 30-37 weeks pregnant, and a study visit 2-8 weeks after you give birth. If you

enroll during your third trimester, you will only have one visit during your pregnancy when you are 30-37 weeks pregnant, as well as the visit 2-8 weeks after you give birth.

At each visit, we will ask you about your health, do a physical exam, and do routine blood tests. We will also draw blood to check how well your body is able to fight infection and, if you are living with HIV, to check the amount of HIV in your blood. The total amount of blood drawn for these tests is about 6-13 mL (1 ¼ to 2 ½ teaspoons), depending on if you are living with HIV or not. You will be given the results of these tests. At each visit you will be asked about taking your medicines.

At each visit, repeat blood samples will also be drawn to measure the amount of TB medicines in your blood. If you are also taking certain HIV medicines, we will also collect repeat blood samples to measure the amount of HIV medicines in your blood. A small plastic catheter (soft tube) will be placed in a vein in your arm during this visit, so that blood can be drawn multiple times, without having to stick you with a needle several times. The tube may stay in place until all of the blood samples are drawn. Depending on the medicine(s) you are taking and the time you usually take them, 7 blood samples over 12 hours or 8 blood samples over 24 hours will be drawn. We will explain to you the blood sampling schedule that will be used for you. Each time, we will draw about 2-4 mL (less than 1 teaspoon) of blood, for a total of between 17-35 mL (about 3 ½ - 7 teaspoons), depending on which TB medicines you are taking, and if you are also taking HIV medicines. These repeat blood samples will only be drawn at a visit if you are still taking the TB medicines that we are studying.

For three days before your visit, you must be sure to take your medicines at the same time each day, but you must **not** take your TB (or HIV) medicine(s) on the day you come to the clinic for your study visit. This is very important. We will help you remember this before the visit.

When you come to the visit, we will place a small catheter (soft tube) into your arm and draw your first blood sample, then you will take your TB medicine(s) (and HIV medicines, if you are taking them), and then we will collect the rest of your blood samples over 12 or 24 hours from the same catheter so we can avoid multiple pokes during the day. You will be asked to tell us the times of your previous two doses of medicines and to describe the time and amount of your previous two meals. Before these repeat blood samples are drawn, the study staff will review with you any dietary recommendations related to the TB or HIV medicines you are taking.

If you have blood samples collected over 24 hours, you may be permitted to remain in the clinic overnight, or you may be able to leave the clinic after your last blood draw before the 24 hour blood draw, in which case you must return for the 24 hour blood draw at the time the clinic tells you to return. Part 2 of this form provides more information about what will happen for you at this clinic.

The **TB medicine** levels testing will be done in batches later in the study, so you and your doctor won't get results of these tests.

If you are also taking certain **HIV medicines**, while you are pregnant, your HIV medicine levels will be reported back to you and your doctor as soon as possible once they have been determined. If these levels are low compared to those in non-pregnant adults, you and your doctor will be told. You may decide, in consultation with your doctor, to adjust the dose of the medicine(s). If you and your doctor choose to change your dose of medicine, you may choose to have your blood checked for medication levels on your new dose of medication. After you give birth, your HIV medicine levels testing will be done in batches later in the study, so you and your doctor won't get results of these tests.

In addition to these visits, there will also be a study visit at the time of delivery (see #8 below) and visits for your baby (see #9 below). For select study sites, there will be additional study visits for you and your baby if you breastfeed your baby. Part 2 of this form will provide details about these additional visits, if this clinic is one of the select study sites.

**8. You will have a study visit at the time of delivery.**

At or near the time of delivery, we will ask you questions about your health, do a physical exam, and do routine blood tests. Blood will also be drawn to check how well your body is able to fight infection, to check the amount of HIV in your blood (if you are living with HIV), and to measure the amount of TB medicines in your blood, as well as HIV medicines if you are taking them. About 11-18 mL of (2 - 3 ½ teaspoons) of blood will be drawn.

Right after your baby is born, a small amount of blood will also be drawn from the umbilical cord that is attached to the placenta after the cord is clamped. This will be used to measure the amount of medicines that get into your baby's blood, but this blood comes from the placenta, and not from your baby. You will be given the results of all tests, except the tests to measure the amount of HIV medicines in your blood and the blood from your umbilical cord.

**9. Your baby will have study visits after birth.**

After your baby is born, your baby will be examined 3 times during the study: from birth to 3 days after birth, 5-9 days after birth, and at 4-6 months of age. During these visits, your baby will be weighed and measured and information about your baby's health will be recorded from his/her medical records. If your baby is healthy enough, we will also collect some blood samples to determine how much of the TB medications that you took during pregnancy got into your baby and how long after birth they are present in your baby's blood. If you are taking certain HIV medicines, we will also be looking at the HIV medicines in the same way. We will ask you about how you feed your baby. Your baby will have blood samples drawn at 3 times between birth and 3 days old, and a fourth sample drawn between 5 and 9 days after birth. About 1 mL (less than ¼ teaspoon) of blood will be collected for each sample. The total amount of blood collected for these tests will be around 4 mL (less than 1 teaspoon). These tests will be done later so you will not receive the results of these tests.

Each of your baby's study visits will last about 30 minutes to 1 hour.

For select sites, there will also be an additional examination if you breastfeed your baby. If these additional examinations will happen here at this site, this will be described more in Part 2 of this form.

**10. Different tests will be done at different laboratories**

We will test some of your samples to check your health at our laboratory. Tests to determine the amount of medicine in your samples or your baby's samples will be done at other laboratories that have special ways of looking at the amount of medicine in the samples. Samples for these tests may be sent to other countries.

**11. If you agree, some of your and your baby's blood will be used for genetic testing.**

If you agree, we will use some of your blood for genetic testing. Also, if you agree, we will collect one drop of blood for genetic testing of your baby. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people break down medicines differently and this can change the levels of the medicines in their bodies. If you agree, your and your child's blood would only be used to look at differences in specific genes that may affect the levels of some medicines. Testing of all of your or your child's genes, which is sometimes called whole genome sequencing, will not be done. You may decide that you do not want genetic testing for you or your baby. You may change your decision about having genetic testing at any time by contacting the study clinic. You can still join in this study even if you do not agree to genetic testing. This test will be done later in the study, so you will not receive the results of this test, and the results will not go into your medical records or have your name attached to them.

**Please write your initials or make your mark below to indicate your decision about genetic testing.**

**For YOUR optional genetic testing:**

\_\_\_\_\_ I agree to allow testing of my genes that can affect the levels of medicines in the body.

\_\_\_\_\_ I do not agree to allow testing of my genes.

**For YOUR BABY'S optional genetic testing:**

\_\_\_\_\_ I agree to allow testing of my baby's genes that can affect the levels of medicines in the body.

\_\_\_\_\_ I do not agree to allow testing of my baby's genes.

**12. We may take you or your baby off of the study early.**

The study doctor may need to take you and your baby off the study early without your permission if:

- The study is stopped for any reason.
- You are/your baby is not able to attend the study visits as required by the study.
- We determine that staying in the study might harm you or your baby.

If you must stop taking the TB medicine(s) before the study is over, we may ask you to continue to be part of the study and return for the scheduled study visits and some of the procedures. If you stop the study TB medicines, we also may ask that your baby stay in the study and complete the scheduled study visits and some of the procedures as described in #9 above.

**13. Please tell us if you want to leave the study.**

You and your baby are free to leave the study at any time for any reason. The care that you receive at this clinic will not be affected, but it is important for us to know about your decision.

***Risks of the study***

Taking part in this study may involve some risks and discomfort.

**14. Risk from blood draws**

Blood drawing may cause fainting, lightheadedness or some discomfort. Other risks include bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or swelling of the surrounding skin may occur. There is also a small risk of a minor infection at the blood draw site. Blood drawing from your baby can also be done by heel stick. Heel stick may cause some discomfort, bleeding or bruising at the site of the heel stick. There is a small risk of infection at the site of the heel stick.

**15. There could be risks of disclosure of your information.**

We will make every effort to keep your and your baby's information private and confidential. Study records and specimens will be kept in secure, locked locations. All specimens and most records will be labeled only with a code number. However, your name will be written on some records.

Despite our best efforts to keep your information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stress or embarrassment.

***Benefits of the study***

**16. There may be no direct benefit to you or your baby from being in the study.**

If you take part in this study, there may be no direct benefit to you or your baby. You may benefit from having the levels of HIV medicine(s) in your blood measured and having your blood checked for safety effects. Information learned from this study may help others who have HIV and tuberculosis.

***Other information about the study***

**17. There are no costs from being in the study.**

There is no cost for the study-related clinic visits, examinations, and laboratory tests in this study.

**18. Study records may be reviewed by study staff and groups that oversee the study.**

Groups that oversee the study include:

- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your or your baby's name or identify you or your baby personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you or your baby. At most, the website will include a summary of the results. You can search this website at any time. If you want the results from this study, please tell the study staff.

Your or your baby's study information may be given to other authorities if required by law.

**19. What will happen with your data and specimens after the study.**

The samples collected from you and your baby will only be used for the testing described in this form. The samples will not be used for other research now or in the future. The samples will not be sold or used for commercial profit. For example, the samples will not be used to make a new product that could be sold.

Other information collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about HIV. Any future research done with the information from this study must be approved by the IMPAACT Network. If any future research is done, information about you or your baby may be used. Your or your baby's information will be labeled with a code number, and the only link between the code number and your name or your baby's name will be kept at this site. Your name or your baby's name will not be given to other researchers.

Data or information from the study may be shared with drug companies who have agreements with the IMPAACT Network and/or the U.S. NIH, or regulatory entities, but you or your baby will never be identified personally.

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

## Appendix VI-D Part 2: SITE-SPECIFIC Consent Information for Participation in Component 4

### PART 2: SITE-SPECIFIC CONSENT INFORMATION

**Site Name:**

**Study Title:** IMPAACT 2026: Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum, Version 1.0, 22 January 2020

JHM IRB Application Number: <<US sites only.>>

**Site Investigator of Record:**

**Site Principal Investigator Contact Information:**

**Emergency Contact:**

**Other Study Contact(s):**

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#### Introduction

This study is being done at multiple sites. This part of the consent form includes information about your site and is specific to participation at your site only. Before making your decision, both the site-specific information and general study information will be reviewed with you. You will have the opportunity to discuss any questions, including questions about this portion of the consent document, with your site's study team.

#### Site-Specific Study Procedures and Associated Risks

***Procedures for Repeat Blood Samples***

As described in Part 1 #7 of this form, we will collect repeat blood samples from you several times over 24 hours at up to two visits during your pregnancy and one visit after you give birth.

<<Sites should select one of the following descriptions of procedures for intensive PK blood samples collected over 24 hours, to clarify the information provided in #7 of Part 1 and to specify what will happen for participants at your site. Sites may modify the description if necessary, to further make site specific or provide any additional details relevant to the local context.>>

*Example 1:* For these visits, you will need to stay throughout the day and overnight at the clinic or hospital for up to 24 hours.

*Example 2:* For these visits, you will stay in the clinic or hospital through the second-to-last blood draw (the blood draw before your final blood draw at 24 hours), but you can go home after that and return to the clinic the next day for the final 24-hour blood draw. It is also possible to have room accommodations made within walking distance to the clinic or hospital for this visit.

***Additional Study Visits for Women who Breastfeed their Baby***



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<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

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<<Sites may choose to participate or not participate in breast milk transfer PK evaluations based on local standard of care breastfeeding practices. Sites must select one of the following two options of text based on this determination.>>

<<**Option 1: For sites where breastfeeding is standard practice, include the following information.**>>

This site is one of the select sites that will look at how much of the TB medicines get into a mother's breast milk, and then into a baby's blood from drinking the breast milk, among women who breastfeed their baby after delivery. If you breastfeed your baby after she/he is born, and if your baby is healthy, you will also have study visits with your baby at 5-9 days after birth and 4-6 months after birth, and your baby will have an additional visit with you at 2-8 weeks after birth. At each of these visits, we will ask you about your health, do a physical exam, weigh and measure your baby, and record information about your baby's health from her/his medical records. If we are not already drawing blood to measure the amount of TB medicines in your blood as part of the study visit, we will draw a blood sample from you and your baby.

- For you, at 5-9 days after birth and 4-6 months after birth, we will draw one blood sample at each visit. Depending on which medicines you are taking, 2-4 mL (less than 1 teaspoon) of blood will be collected.
- For your baby, about 1 mL (less than ¼ teaspoon) of blood will be drawn at 2-8 weeks after birth and at 4-6 months after birth.
- We will also collect a breast milk sample from you at the visits at 5-9 days after birth, 2-8 weeks after birth, and 4-6 months after birth.

From all of these samples, we will measure the amount of TB medicines in your blood, in your baby's blood, and in your breast milk, to determine how much of the medicine that you take gets into your baby through drinking breast milk. If you have HIV and are taking certain HIV medicines, we will measure the amount of HIV medicines in the same way.

Each of the extra visits for you and your baby will last about <<sites add local information about time for study visits>>.

For three days before your visit, you must be sure to take your medicines at the same time each day. This is very important. We will help you remember this before the visit.

We will only collect these extra samples and have these extra visits if you are breastfeeding your baby at the time of the visit. If you do not breastfeed your baby or are no longer breastfeeding your baby at the time of the visit, we will not do these extra visits or collect the extra samples for breast milk testing. These tests will be done later in the study so you will not receive the results.

<< **Option 2: For sites where breastfeeding is NOT standard practice, include the following information.**>>

This site is not one of the select sites that will look at the amount of TB medicines in breast milk that get into a baby's blood. All of the study visits you and your baby will have are described in Part 1 of this form.

### **Costs to Study Participants:**

<<Brief description of costs to participants. Only include if different than costs as described in the main consent document.>>

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

*Example:* Any medical costs for your treatment outside this study, including your prescribed medicines for HIV, will be charged to you or your health insurance company. This study will not cover any cost related to your pregnancy and delivery or care of your baby.

**Payment for Study Participation:**

<<Brief description of payments and/or reimbursements.>>

**Compensation for Research-Related Injury:**

Your health is important to us. We will make every effort to protect your and your baby's well-being and minimize risks.

<<Add any locally-required language for research-related injury and contact information outlining who subjects should call in the event of any research-related injuries. Information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement about no compensation through the US NIH is mandatory for all sites and may not be deleted.>>

If you are/your baby is injured as a result of being in this study, you/your baby will be given immediate treatment for your/your baby's injuries. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation through the United States National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

**Certificate of Confidentiality**

<<U.S. SITES only MUST include, sites outside of the U.S. MUST delete Certificate of Confidentiality section:>>

To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify you or your baby, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you or your baby. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

**Contact Information:**

**If you have questions, concerns, or problems at any time, use these contacts.**

- If you have questions about the study:  
<< insert name and telephone number of investigator or other study staff >>
- If you or your baby have any health or other problems that may be related to study participation:  
<< insert name and telephone number of investigator or other study staff >>
- If you want to leave the study:  
<< insert name and telephone number of investigator or other study staff >>

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

- << *Non-U.S. sites should modify the following as appropriate.* >> This study has been reviewed by an Institutional Review Board (IRB), a group of people that reviews human research studies. The IRB protects the rights and welfare of the people taking part in those studies. The IRB can help you if you have questions about your or your child's rights as a research participant or if you have other questions, concerns or complaints about this research study. If you have questions about your or your baby's rights as research participants or concerns about how you are/your baby is being treated in the study:
  - For this multi-site study, Johns Hopkins has agreed to serve as the single IRB (sIRB) providing oversight for all sites in the U.S. You may contact the Johns Hopkins IRB at **410-502-2092** or **jhmeirb@jhmi.edu** with your questions or concerns.
  - You may also contact the [site specific IRB contact information] with your questions or concerns. << *If your site wishes to include local IRB contact information, please include this here. If this is not required, please delete this section.* >>

#### **Additional information about your local site:**

<<Please insert any additional required language for your site, as applicable for this study. Examples may include

- *Local regulatory authorities that may review study records (in addition to those listed in Part 1 #18)*
- *Local language regarding state law requirements for reporting of communicable diseases or other mandated reporting requirements*
- *Locally required language for any specific research procedures, e.g. commercialization of cell lines*
- *Local conflict of interest disclosures*

#### **How will your privacy be maintained and how will the confidentiality of your data be protected?**

<< Insert locally-required HIPAA authorization language. The following language has already been approved by the JHM IRB. Please consider whether this language may be used at your site:

- *If this language is acceptable, it may remain in this section.*
- *If this language is not acceptable, and locally-approved HIPAA authorization language is required, please delete the language and replace it with your own language.*
- *Alternatively, if your site requires use of a separate HIPAA authorization, please delete this section and include the following sentence: "[Add site name] requires that you sign a separate authorization form related to the use of your protected health information for this research study. This is required for participation in this study." >>*

#### **HIPAA Authorization for Disclosure of Protected Health Information**

#### **What information is being collected, used, or shared?**

To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

#### **Who will see, use or share the information?**

The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at << *insert site name* >>, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

share your information with others outside of << insert site name >>. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

**Do you have to sign this Authorization?**

You do not have to sign this Authorization, but if you do not, you may not join the study.

**How long will your information be used or shared?**

Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

**What if you change your mind?**

You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

**Signature Lines:**

*<<US sites: If your site wishes to include site-specific signature lines, please include them here. If your site does not have site-specific signature requirements, the JHM IRB signature lines will be added in this section.*

*Non-US sites: If your site wishes to include site-specific signature lines, please include them here. If your site does not have site-specific signature requirements, please use the template lines provided below. >>*

**If you agree to participate in this study, please sign or make your mark below.**

_____	_____	_____
Name of Participant (print)	Signature of Participant	Date

_____	_____	_____
Name of Study Staff Conducting Consent Process Name (print)	Signature of Study Staff	Date

_____	_____	_____
Name of Witness (as appropriate; print)	Signature of Witness	Date

## Appendix VI-E Part 1: MASTER Sample Informed Consent Form for Participation in Component 5

*[U.S. sites may NOT modify Part 1]*

### **IMPAACT 2026 Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum**

**Version 1.0, 22 January 2020**

#### ***Introduction***

You and your baby are being asked to take part in the research study named above because you are breastfeeding your baby and are taking one of the following HIV medicines while you are breastfeeding: **atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir.**

This consent form gives information about this study. Please read it, or have it read to you, and ask any questions you may have. You may have as much time as needed to fully understand the study. We will ask you questions to see if we have explained the study clearly.

This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study, this informed consent form includes two parts. Part 1 of the consent form includes general study information that applies to all study sites. Part 2 of the consent form includes information specific to the study site where you are being asked to enroll. Before making your decision, both parts of this form will be reviewed with you. You will have the opportunity to discuss any questions about this form and both of its parts with your site's study team.

#### ***Key Information***

Here is a summary of important information about the study:

- The primary purpose of the study is to determine how much of the HIV medicines are in the blood and breast milk of women who are taking them while breastfeeding, and in the blood of their babies. Another purpose is to look at how safe the medicines are for mother and baby.
- If you choose to join the study, you and your baby will have your first visit about a week after you give birth and will stay in the study for about 6 months. You and your baby will have three study visits.
- You will continue to receive the HIV medicines given by your health care provider.
- You and your baby will have blood drawn at each study visit to measure the amount of HIV medicines in your blood, and you will have breast milk collected. You will be asked questions about your and your baby's health and you and your baby will have physical exams.
- There may be no direct benefit to you or your baby from being in the study. However, this study may help doctors learn information that will help in the treatment of future patients with HIV who are breastfeeding.
- The most likely risk to you and your baby is from blood drawing- including pain, which is usually minor, and infection, which is rare.

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

- Your decision will have no effect on the medical care that you and your baby would normally receive from your clinic. Your access to services, and the benefits and rights you normally have, will not be affected.

More information is given in both parts of this form about the study, its risks and benefits. You should feel that you understand the study before deciding whether you and your baby will participate.

After you understand the study, and if you decide that you and your baby will join the study, you will be asked to sign or make your mark on this form. You will be offered a copy to keep. You do not give up any rights by signing this form.

### **About the study**

This study is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT).

The study will measure the amounts of certain HIV medicines in the breast milk and blood of women who are taking these medicines while breastfeeding, and it will also measure the amount of these medicines in the blood of their babies. The study will include up to 15 mothers and their babies for each medicine or combination of medicines that we are looking at, from Botswana, Brazil, India, Kenya, Malawi, South Africa, Tanzania, Thailand, Uganda, Zimbabwe, and the United States. You and your baby will be in the study for up to 24 weeks after your baby is born.

The United States National Institutes of Health are paying for this study.

#### **1. The study will measure the amounts of HIV medicines in the blood and breast milk of women who are taking them while breastfeeding, and in the blood of their babies.**

Mothers who need to take medicines to treat their HIV may also need to or want to breastfeed their babies. Not much is known about how much certain HIV medicines that nursing mothers take get from the mother's breast milk into her baby's blood. In this study, we will look at the levels of these medicines in your blood and your breast milk, compared to the levels of the medicine(s) in your baby's blood. We will also look at how safe these medicines are for you and your baby.

#### **2. Only women and their babies who are eligible can join the study.**

If you decide to join the study with your baby, we will first talk to you about the study and collect some information about you and your baby to find out if you are both eligible. More information about this is given in section #4 below. If you and your baby are eligible, you can join into the study. If either you or your baby are not eligible, you cannot join the study.

#### **3. It is your decision whether or not you join the study.**

Deciding to join the study is voluntary (your choice). If you and your baby are eligible, you can choose if you want to join the study or not. You are free to join or not join. If you join, you must agree for your baby to join the study too. If you and your baby join, you can change your mind later and leave the study. Your decision will have no effect on the medical care that you and your baby would normally receive

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

from your clinic. Your access to services, and the benefits and rights you normally have, will not be affected. If you decide to join, we will tell you any new information from this study or other studies that may affect your willingness to stay in the study. You are welcome to ask questions or request more information at any time.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. You can bring other people here to learn about the study with you.

### ***Finding out if You and Your Baby are Eligible for the Study***

#### **4. We will ask you questions, look at your medical records, and discuss the study with you.**

You will need to come to the clinic to make sure you and your baby are eligible for the study before you both join. This may be done as part of your first study visit for this study or during a routine care visit, so a separate visit may not be required. To find out if you can join, we will talk to you about what you and your baby will have to do if you decide to join the study, and we will also talk to you about your plans for breastfeeding your baby. We will collect some information from your medical records about you, your health, your pregnancy and birth, and the medications that you take. We may test your blood for HIV to confirm your status. If we test your blood for HIV, we will give you the results. We will also collect some information from your baby's medical records about your baby's health and medications. We will tell you if you and your baby are or are not eligible for the study.

### ***Entering the study***

#### **5. If you are eligible, you and your baby will enter the study about a week after you have your baby.**

Mothers and their babies can only join the study between 5 and 9 days after their baby is born. If you are eligible, we will tell you if it is the right time to enter the study. The day you join the study will be the day of your first study visit.

### ***Being in the Study***

#### **6. You will continue to take your HIV medicines.**

If you join the study, you will continue to receive and take your HIV medicines as you normally would. No medicines are supplied by this study. It will be important for you to continue with all of your regular HIV care even if you join the study.

#### **7. You and your baby will have three study visits.**

You will have a total of 3 study visits with your baby, at the following times:

- Between 5 and 9 days after birth
- Between 2 and 12 weeks after birth,
- Between 4 and 6 months after birth.

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<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

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JHM IRB Application No.:

At each of these visits, we will ask you about your health, do a physical exam for you, weigh and measure your baby, and record information about you and your baby's health from medical records. We will talk to you about how you are feeding your baby. We will draw one blood sample from you that is 2 mL (less than ½ teaspoon) at each visit. For your baby, we will draw one blood sample that is 0.75 mL (a few drops) of blood at each visit. We will also collect a breast milk sample from you at each visit. We will use all of these samples to measure the amount of HIV medicine in your blood, in your baby's blood, and in your breast milk, to determine how much of these medicines that you are taking are getting into your baby's blood through your baby drinking your breast milk. These tests will be done later in the study so you will not receive the results.

Each of these visits for you and your baby will last about 1 hour.

You and your baby will only have these visits and blood drawn if you are breastfeeding your baby at the time of the visit. If you stop breastfeeding your baby after you have joined the study but before your study visits are over, you will not have any more study visits.

**8. Different tests will be done at different laboratories**

We will test some of your samples to check your health at our laboratory. Tests to determine the amount of medicine in your samples or your baby's samples will be done at other laboratories that have special tests for this. Samples for these special tests may be sent to laboratories in other countries.

**9. If you agree, some of your and your baby's blood will be used for genetic testing.**

If you agree, we will use some of your blood for genetic testing. Also, if you agree, we will collect one drop of blood for genetic testing of your baby. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people break down medicines differently and this can change the levels of the medicines in their bodies. If you agree, your and your child's blood would only be used to look at differences in specific genes that may affect the levels of some medicines. Testing of all of your or your child's genes, which is sometimes called whole genome sequencing, will not be done. You may decide that you do not want genetic testing for you or your baby. You may change your decision about having genetic testing at any time by contacting the study clinic. You can still join in this study even if you do not agree to genetic testing. This test will be done later in the study, so you will not receive the results of this test, and the results will not go into your medical records or have your name attached to them.



**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

**Please write your initials or make your mark below to indicate your decision about genetic testing.**

**For YOUR optional genetic testing:**

\_\_\_\_\_ I agree to allow testing of my genes that can affect the levels of medicines in the body.

\_\_\_\_\_ I do not agree to allow testing of my genes.

**For YOUR BABY'S optional genetic testing:**

\_\_\_\_\_ I agree to allow testing of my baby's genes that can affect the levels of medicines in the body.

\_\_\_\_\_ I do not agree to allow testing of my baby's genes.

**10. We may take you and your baby off of the study early.**

The study doctor may need to take you and your baby off the study early without your permission if:

- The study is stopped for any reason.
- You are/your baby is not able to attend the study visits as required by the study.
- You are not able to take the HIV medicine(s) required by the study.
- You are not able to continue breastfeeding your baby.
- We determine that staying in the study might harm you or your baby.

**11. Please tell us if you want to leave the study.**

You and your baby are free to leave the study at any time for any reason. The care that you receive at this clinic will not be affected, but it is important for us to know about your decision.

***Risks of the study***

Taking part in this study may involve some risks and discomfort.

**12. Risk from blood draws**

Blood drawing may cause fainting, lightheadedness or some discomfort. Other risks include bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or swelling of the surrounding skin may occur. There is also a small risk of a minor infection at the blood draw site. Blood drawing from your baby can also be done by heel stick. Heel stick may cause some discomfort, bleeding or bruising at the site of the heel stick. There is a small risk of infection at the site of the heel stick.

**13. There could be risks of disclosure of your information.**

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

We will make every effort to keep your and your baby's information private and confidential. Study records and specimens will be kept in secure, locked locations. All specimens and most records will be labeled only with a code number. However, your name will be written on some records.

Despite our best efforts to keep your information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stress or embarrassment.

### ***Benefits of the study***

**14. There may be no direct benefit to you or your baby from being in the study.**

If you take part in this study, there may be no direct benefit to you or your baby. Information learned from this study may help others who breastfeed their babies and take these medicines in the future.

### ***Other information about the study***

**15. There are no costs from being in the study.**

There is no cost for the study-related clinic visits, examinations, and laboratory tests in this study.

**16. Study records may be reviewed by study staff and groups that oversee the study.**

Groups that oversee the study include:

- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your or your baby's name or identify you or your baby personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you or your baby. At most, the website will include a summary of the results. You can search this website at any time. If you want the results from this study, please tell the study staff.

Your or your baby's study information may be given to other authorities if required by law.

**Do not use this form for consenting research participants unless a stamp appears here.**

*<<US sites only.>>*

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

**17. What will happen with your data and specimens after the study.**

The samples collected from you and your baby will only be used for the testing described in this form. The samples will not be used for other research now or in the future. The samples will not be sold or used for commercial profit. For example, the samples will not be used to make a new product that could be sold.

Other information collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about HIV. Any future research done with the information from this study must be approved by the IMPAACT Network. If any future research is done, information about you or your baby may be used. Your or your baby's information will be labeled with a code number, and the only link between the code number and your name or your baby's name will be kept at this site. Your name or your baby's name will not be given to other researchers.

Data or information from the study may be shared with drug companies who have agreements with the IMPAACT Network and/or the U.S. NIH, or regulatory entities, but you or your baby will never be identified personally.

**Do not use this form for consenting research participants unless a stamp appears here.**

*<<US sites only.>>*

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

## **Appendix VI-E Part 2: SITE-SPECIFIC Consent Information for Participation in Component 5**

### **PART 2: SITE-SPECIFIC CONSENT INFORMATION**

**Site Name:**

**Study Title:** IMPAACT 2026: Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum, Version 1.0, 22 January 2020

JHM IRB Application Number: *<<US sites only.>>*

**Site Investigator of Record:**

**Site Principal Investigator Contact Information:**

**Emergency Contact:**

**Other Study Contact(s):**

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#### **Introduction**

This study is being done at multiple sites. This part of the consent form includes information about your site and is specific to participation at your site only. Before making your decision, both the site-specific information and general study information will be reviewed with you. You will have the opportunity to discuss any questions, including questions about this portion of the consent document, with your site's study team.

**Costs to Study Participants:**

*<<Brief description of costs to participants. Only include if different than costs as described in the main consent document. >>*

*Example:* Any medical costs for your treatment outside this study, including your prescribed medicines for HIV, will be charged to you or your health insurance company. This study will not cover any cost related to your pregnancy and delivery or care of your baby.

**Payment for Study Participation:**

*<<Brief description of payments and/or reimbursements.>>*

**Compensation for Research-Related Injury:**

Your health is important to us. We will make every effort to protect your and your baby's well-being and minimize risks.

*<<Add any locally-required language for research-related injury and contact information outlining who subjects should call in the event of any research-related injuries. Information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement about no compensation through the US NIH is mandatory for all sites and may not be deleted.>>*

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

If you are/your baby is injured as a result of being in this study, you/your baby will be given immediate treatment for your/your baby's injuries. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation through the United States National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

### **Certificate of Confidentiality**

<<U.S. SITES only MUST include, sites outside of the U.S. MUST delete Certificate of Confidentiality section:>>

To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify you or your baby, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you or your baby. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

### **Contact Information:**

**If you have questions, concerns, or problems at any time, use these contacts.**

- If you have questions about the study:  
<< insert name and telephone number of investigator or other study staff >>
- If you or your baby have any health or other problems that may be related to study participation:  
<< insert name and telephone number of investigator or other study staff >>
- If you want to leave the study:  
<< insert name and telephone number of investigator or other study staff >>
- << Non-U.S. sites should modify the following as appropriate.>> This study has been reviewed by an Institutional Review Board (IRB), a group of people that reviews human research studies. The IRB protects the rights and welfare of the people taking part in those studies. The IRB can help you if you have questions about your or your child's rights as a research participant or if you have other questions, concerns or complaints about this research study. If you have questions about your or your baby's rights as research participants or concerns about how you are/your baby is being treated in the study:
  - For this multi-site study, Johns Hopkins has agreed to serve as the single IRB (sIRB) providing oversight for all sites in the U.S. You may contact the Johns Hopkins IRB at **410-502-2092** or **jhmeirb@jhmi.edu** with your questions or concerns.
  - You may also contact the [site specific IRB contact information] with your questions or concerns. << If your site wishes to include local IRB contact information, please include this here. If this is not required, please delete this section. >>

### **Additional information about your local site:**

<<Please insert any additional required language for your site, as applicable for this study. Examples may include

- Local regulatory authorities that may review study records (in addition to those listed in Part 1 #18)

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

- *Local language regarding state law requirements for reporting of communicable diseases or other mandated reporting requirements*
- *Locally required language for any specific research procedures, e.g. commercialization of cell lines*
- *Local conflict of interest disclosures*

### **How will your privacy be maintained and how will the confidentiality of your data be protected?**

<< Insert locally-required HIPAA authorization language. The following language has already been approved by the JHM IRB. Please consider whether this language may be used at your site:

- *If this language is acceptable, it may remain in this section.*
- *If this language is not acceptable, and locally-approved HIPAA authorization language is required, please delete the language and replace it with your own language.*
- *Alternatively, if your site requires use of a separate HIPAA authorization, please delete this section and include the following sentence: “[Add site name] requires that you sign a separate authorization form related to the use of your protected health information for this research study. This is required for participation in this study.” >>*

### **HIPAA Authorization for Disclosure of Protected Health Information**

#### **What information is being collected, used, or shared?**

To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

#### **Who will see, use or share the information?**

The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at << insert site name >>, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of << insert site name >>. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

#### **Do you have to sign this Authorization?**

You do not have to sign this Authorization, but if you do not, you may not join the study.

#### **How long will your information be used or shared?**

Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

#### **What if you change your mind?**

You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

**Signature Lines:**

*<<US sites: If your site wishes to include site-specific signature lines, please include them here. If your site does not have site-specific signature requirements, the JHM IRB signature lines will be added in this section.*

*Non-US sites: If your site wishes to include site-specific signature lines, please include them here. If your site does not have site-specific signature requirements, please use the template lines provided below. >>*

**If you agree to participate in this study, please sign or make your mark below.**

\_\_\_\_\_  
Name of Participant  
(print)

\_\_\_\_\_  
Signature of Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Study Staff Conducting  
Consent Process Name (print)

\_\_\_\_\_  
Signature of Study Staff

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Witness  
(as appropriate; print)

\_\_\_\_\_  
Signature of Witness

\_\_\_\_\_  
Date

## **Appendix VII: Sample Parent/Guardian Consent Forms**

### **Appendix VII-A Part 1: MASTER Sample Parent/Guardian Informed Consent Form for Participation in Component 2**

*for parents/guardians of adolescents who cannot provide independent informed consent for study participation*

*[U.S. sites may NOT modify Part 1 of this consent form]*

### **IMPAACT 2026 Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum**

**Version 1.0, 22 January 2020**

#### ***Introduction***

Your child is being asked to take part in the research study named above because she is pregnant and has received at least one injection with the long-acting drug cabotegravir (CAB LA) during her pregnancy as part of participation in a different research study.

This consent form gives information about this study. Please read it, or have it read to you, and ask any questions you may have. You may have as much time as needed to fully understand the study. We will ask you questions to see if we have explained the study clearly.

This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study, this informed consent form includes two parts. This part of the consent form includes general study information that applies to all study sites. The second part of the consent form includes information specific to the study site where your child is being asked to enroll. Before making your decision, both parts of this form will be reviewed with you. You will have the opportunity to discuss any questions about this form and both of its parts with your site's study team.

#### ***Key Information***

Here is a summary of important information about the study:

- The primary purpose of the study is to determine how much of the CAB LA that a woman received during pregnancy gets into her baby after delivery. Another purpose is to look at how safe the medicines are for mother and baby.
- If you choose to allow your child to join the study, she will have her first study visit before she gives birth and will have a study visit at delivery. Her baby will be in the study for at least about two weeks after birth and will have at least three study visits.
- She will have blood drawn at each study visit after the first visit, to measure the amount of injectable cabotegravir in her blood, and her baby may have blood drawn at each visit too. She will be asked questions about her and her baby's health and she and her baby will have physical exams and routine blood tests.
- At select sites, women who breastfeed their baby will have breast milk collected and a couple extra study visits.
- There may be no direct benefit to your child or her baby from being in the study. However, this study may help doctors learn information that will help future patients who receive cabotegravir injections.



- The most likely risk to your child and her baby is from blood drawing- including pain, which is usually minor, and infection, which is rare.
- Your decision will have no effect on the medical care that your child and her baby would normally receive from this clinic. Your child's access to services, and the benefits and rights she normally has, will not be affected.

More information is given in both parts of this form about the study, its risks and benefits. You should feel that you understand the study before deciding whether your child and her baby will participate.

After you understand the study, and if you decide that your child and her baby will join, you will be asked to sign or make your mark on this form. You will be offered a copy to keep. You and your child do not give up any rights by signing this form.

### ***About the study***

This study is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network.

The study will measure the amounts of CAB LA in the blood of women who received it during pregnancy, and it will also measure the amount of CAB LA in the blood of their babies. At some sites, the study will also measure the amounts of CAB LA in the breast milk of women who choose to breastfeed. The study will include up to 28 mothers and their babies who received at least one injection of CAB LA during pregnancy, from Botswana, Brazil, India, Kenya, Malawi, South Africa, Tanzania, Thailand, Uganda, Zimbabwe, and the United States.

The United States National Institutes of Health are paying for this study.

#### **1. The study will measure the amounts of CAB in the blood of women who received it during pregnancy, and in the blood of their babies.**

Your child is already participating in another study of a new drug called CAB LA, which is an anti-HIV drug that may help to protect people from getting HIV and treat people who have HIV. Because it is a new drug, not much is known yet about the amount of CAB LA that gets from a mother's blood into her baby during pregnancy and how long the CAB LA is present in the infant. In this study, we will look at the levels of CAB LA in blood from your child's baby's umbilical cord and compare it to the amount of medicine in your child's blood at the time of delivery. We will also look to see how much of the CAB LA that your child received during pregnancy is present in the baby at birth and for a couple weeks after birth, and how safe these medicines are for your child and her baby. At select study sites, for women who breastfeed their baby, we will also look to see how much of the CAB LA is in their breast milk, and how much gets from their breast milk into their baby's blood.

#### **2. Only pregnant women who are eligible can join the study.**

If you decide to allow your child to join the study with her baby, we will first talk to you and your child about the study and collect some information about your child to find out if she is eligible. More information about this is given in section #4 below. If you she is eligible, she can join the study. If she is not eligible, she cannot join the study.

**3. It is your decision whether or not your child joins the study.**

Deciding to join the study is voluntary (your choice). If your child is eligible, you can choose to allow your child to join or not join. Your child will also be asked if she wants to join the study. You and your child must both agree. If your child joins, you and your child must both agree for her baby to join the study too. If your child and her baby join, you or she can change your/her mind later and leave the study. Your decision will have no effect on the medical care that your child and her baby would normally receive from this clinic. Your child's access to services, and the benefits and rights your child normally has, will not be affected. If you decide to allow your child to join, we will tell you and your child any new information from this study or other studies that may affect your willingness for your child to stay in the study. You and your child are welcome to ask questions or request more information at any time.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. You can bring other people here to learn about the study with you.

***Finding out if Your Child and Her Baby are Eligible for the Study***

**4. We will ask you and your child questions, look at your child's medical records, and discuss the study with you and your child.**

Your child will need to come to the clinic to make sure she is eligible for the study before she joins. This may be done as part of her first study visit for this study or during her routine study visit for HPTN 084 or IMPAACT 2017, so a separate visit may not be required, but this must be done before she has her baby. To find out if your child can join, we will talk to you and your child about what she will have to do if you decide to allow her to join the study. We will collect some information from your child's medical records about your child, her health, her pregnancy, and the medications that she takes. We will tell you if your child is or is not eligible for the study.

***Entering the study***

**5. If your child is eligible, she will enter the study during her pregnancy before she has her baby.**

Women can only join the study when they are at least 24 weeks pregnant but have not yet delivered their baby. If your child is eligible, we will tell you if it is the right time to enter the study.

**6. Your child will have one study visit when she enters the study before she gives birth.**

Your child will have a study visit when she enters the study, before she gives birth. At this visit, we will ask her about her health and do a physical exam. We will not draw any blood at this visit. This visit may also be done as part of a routine study visit for HPTN 084 or IMPAACT 2017, or it may be combined with the visit to find out if she is eligible for the study, so a separate visit may not be required.

***Being in the Study***

**7. Your child will have a study visit at the time of delivery.**

At or near the time of delivery, we will ask your child questions about her health, do a physical exam, and do routine blood tests. Blood will also be drawn to measure the amount of CAB LA in her blood. A total of about 13 mL (a little under 3 teaspoons) of blood will be drawn.

Right after your child's baby is born, a small amount of blood will also be drawn from the umbilical cord that is attached to the placenta after the cord is clamped and cut. This blood comes from the placenta, and not from the

baby. This will be used to measure the amount of medicines that get into the baby's blood, but this blood comes from the placenta, and not from the baby.

You will be given the results of the routine blood tests. The tests to measure the amount of medicine levels in your child's blood and her baby's blood will be done later in the study, so you won't get results of these tests.

**8. Your child's baby will have study visits after birth.**

After the baby is born, the baby will be examined at least 3 times during the study: from birth to 3 days after birth, 5-9 days after birth, and 12-16 days after birth. During these visits, the baby will be weighed and measured and information about the baby's health will be recorded from his/her medical records. Your child's baby, if healthy enough, will have blood samples drawn to determine how much of the CAB LA that your child received during pregnancy got into the baby's blood and how long it takes to get out. We will ask your child about how she feeds her baby. Her baby will have blood samples drawn at 3 times between birth and 3 days old, a fourth sample drawn between 5-9 days after birth and a fifth sample drawn at 12-16 days after birth. Less than 1 mL (less than ¼ teaspoon) of blood will be collected for each sample. The total amount of blood collected for these tests will be around 4 mL (less than 1 teaspoon). These blood tests will be done later in the study too, so you will not receive the results of these tests.

For select study sites, there will be additional study visits for your child and her baby if she breastfeeds her baby after birth. Part 2 of this form will provide details about these additional visits, if this clinic is one of the select study sites.

**9. Different tests will be done at different laboratories**

We will test some of your child's samples to check her health at our laboratory. Tests to determine the amount of medicine in your child's samples or her baby's samples will be done at other laboratories that have special tests for this. Samples for these special tests may be sent to laboratories in other countries.

**10. If you agree, some of your child and her baby's blood will be used for genetic testing.**

If you agree, we will use some of your child's blood for genetic testing. Also, if you agree, we will collect one drop of blood for genetic testing of her baby. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people break down medicines differently and this can change the levels of the medicines in their bodies. If you agree, your child and her baby's blood would only be used to look at differences in specific genes that may affect the levels of some medicines. Testing of all of your child's and her baby's genes, which is sometimes called whole genome sequencing, will not be done. You may decide that you do not want genetic testing for your child or her baby. You may change your decision about having genetic testing at any time by contacting the study clinic. Your child can still join in this study even if you do not agree to genetic testing. This test will be done later in the study, so you will not receive the results of this test, and the results will not go into your child's medical records or have her name attached to them.

**Please write your initials or make your mark below to indicate your decision about genetic testing.**

**For YOUR CHILD'S optional genetic testing:**

\_\_\_\_\_ I agree to allow testing of my child's genes that can affect the levels of medicines in the body.

\_\_\_\_\_ I do not agree to allow testing of my child's genes.

**For YOUR CHILD'S BABY'S optional genetic testing:**

\_\_\_\_\_ I agree to allow testing of the baby's genes that can affect the levels of medicines in the body.

\_\_\_\_\_ I do not agree to allow testing of the baby's genes.

**11. We may take your child or her baby off of the study early.**

The study doctor may need to take your child and her baby off the study early without your permission if:

- The study is stopped for any reason.
- Your child and/or her baby are not able to attend the study visits as required by the study.
- We determine that staying in the study might harm your child or her baby.

**12. Please tell us if you want your child to leave the study.**

Your child and her baby are free to leave the study at any time for any reason. The care that your child receives at this clinic will not be affected, but it is important for us to know about your decision.

***Risks of the study***

Taking part in this study may involve some risks and discomfort.

**13. Risk from blood draws**

Blood drawing may cause fainting, lightheadedness or some discomfort. Other risks include bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or swelling of the surrounding skin may occur. There is also a small risk of a minor infection at the blood draw site. Blood drawing from your child's baby can also be done by heel stick. Heel stick may cause some discomfort, bleeding or bruising at the site of the heel stick. There is a small risk of infection at the site of the heel stick.

**14. There could be risks of disclosure of your child's information.**

We will make every effort to keep your child and her baby's information private and confidential. Study records and specimens will be kept in secure, locked locations. All specimens and most records will be labeled only with a code number. However, your child's name will be written on some records.

Despite our best efforts to keep your child's information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, your child could be treated badly or unfairly. Your child could feel stress or embarrassment.

### ***Benefits of the study***

**15. There may be no direct benefit to your child or her baby from being in the study.**

If your child takes part in this study, there may be no direct benefit to her or her baby. Your child or her baby may benefit from having her or her baby's blood checked for safety effects. Information learned from this study may help others who receive CAB LA in the future.

### ***Other information about the study***

**16. There are no costs from being in the study.**

There is no cost for the study-related clinic visits, examinations, and laboratory tests in this study.

**17. Study records may be reviewed by study staff and groups that oversee the study.**

Groups that oversee the study include:

- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your child's or her baby's name or identify her or her baby personally.

A description of this study will be available on [ClinicalTrials.gov](http://ClinicalTrials.gov) as required by U.S. law. This website will not include information that can identify your child or her baby. At most, the website will include a summary of the results. You can search this website at any time. If you want the results from this study, please tell the study staff.

Your child or her baby's study information may be given to other authorities if required by law.

**18. What will happen with your child's data and specimens after the study.**

The samples collected from your child and her baby will only be used for the testing described in this form. The samples will not be used for other research now or in the future. The samples will not be sold or used for commercial profit. For example, the samples will not be used to make a new product that could be sold.

Other information collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about HIV. Any future research done with the information from this study must be approved by the IMPAACT Network. If any future research is done, information about your child or her baby may be used. Your child or her baby's information will be labeled with a code number, and the only link between the code number and her name or the baby's name will be kept at this site. Your child's name or her baby's name will not be given to other researchers.

Data or information from the study may be shared with drug companies who have agreements with the IMPAACT Network and/or the U.S. NIH, or regulatory entities, but your child or her baby will never be identified personally.

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

**Appendix VII-B Part 2: SITE-SPECIFIC Parent/Guardian Consent Information for Participation in Component 2**

*for parents/guardians of adolescents who cannot provide independent informed consent for study participation*

**PART 2: SITE-SPECIFIC PARENT/GUARDIAN CONSENT INFORMATION**

**Site Name:**

**Study Title:** IMPAACT 2026: Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum, Version 1.0, 22 January 2020

JHM IRB Application Number: <<US sites only.>>

**Site Investigator of Record:**

**Site Principal Investigator Contact Information:**

**Emergency Contact:**

**Other Study Contact(s):**

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**Introduction**

This study is being done at multiple sites. This part of the consent form includes information about your site and is specific to participation at your site only. Before making your decision, both the site-specific information and general study information will be reviewed with you. You will have the opportunity to discuss any questions, including questions about this portion of the consent document, with your site's study team.

**Site-Specific Study Procedures and Associated Risks**

***Additional Study Visits for Women who Breastfeed their Baby***

*<<Sites may choose to participate or not participate in breast milk transfer PK evaluations based on local standard of care breastfeeding practices. Sites must select one of the following two options of text based on this determination.>>*

*<<Option 1: For sites where breastfeeding is standard practice, sites should include the following information.>>*

This site is one of the select sites that will look at how much of the CAB LA gets into a mother's breast milk, and then into a baby's blood from drinking the breast milk, among women who breastfeed their baby after delivery. In addition to the visits that were described in Part 1 of this form, if your child breastfeeds after her baby is born, and if her baby is healthy, she will have three extra visits to look at how much of the CAB LA that she received during your pregnancy gets into her baby's blood through drinking breast milk. These extra visits would be within 5 weeks after giving birth.

Your child will have study visits with her baby at 5-9 days after birth, 12-16 days after birth, and 3-5 weeks after birth. At each of these visits, we will ask her about her health, do a physical exam, weigh and measure her baby,

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<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

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and record information about her baby's health from her/his medical records. We will draw one 2 mL blood sample from your child (less than ½ teaspoon) at each visit. For her baby, we will draw less than 1 mL (less than ¼ teaspoon) of blood at the visit at 3-5 weeks after birth. We will also collect a breast milk sample from your child at the visits at 5-9 days after birth, 12-16 days after birth, and 3-5 weeks after birth.

We will use all of these samples to measure the amount of CAB in your child's blood, in her baby's blood and in her breast milk. We will only collect these extra samples and have these extra visits if your child is breastfeeding her baby at the time of the visit. If she does not breastfeed her baby or is not breastfeeding her baby at the time of the visit, we will not do these extra visits or collect the extra samples for breast milk testing. These tests will be done later in the study, so you will not receive the results.

Each of these visits for your child and her baby will last about <<sites add local information about time for study visits>>.

<< **Option 2:** For sites where breastfeeding is NOT standard practice, include the following information.>>

This site is not one of the select sites that will look at the amount of CAB LA in breast milk that gets into a baby's blood. All of the study visits your child and her baby will have are described in Part 1 of this form.

### **Costs to Study Participants:**

<<Brief description of costs to participants. Only include if different than costs as described in the main consent document. >>

*Example:* Any medical costs for your child's treatment outside this study will be charged to you or your health insurance company. This study will not cover any cost related to your child's pregnancy and delivery or care of her baby.

### **Payment for Study Participation:**

<<Brief description of payments and/or reimbursements.>>

### **Compensation for Research-Related Injury:**

Your child's health is important to us. We will make every effort to protect your child and her baby's well-being and minimize risks.

<<Add any locally-required language for research-related injury and contact information outlining who subjects should call in the event of any research-related injuries. Information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement about no compensation through the US NIH is mandatory for all sites and may not be deleted.>>

If your child/her baby is injured as a result of being in this study, she/her baby will be given immediate treatment for their injuries. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation through the United States National Institutes of Health (NIH). You will not be giving up any of your or your child's legal rights by signing this consent form.

### **Certificate of Confidentiality**

<<U.S. SITES only MUST include, sites outside of the U.S. MUST delete Certificate of Confidentiality section:>>



**Do not use this form for consenting research participants unless a stamp appears here.**

*<<US sites only.>>*

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

To help us protect your child's privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify your child or her baby, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify your child or her baby. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your child's participation in the study to others, if you wish.

### **Contact Information:**

**If you have questions, concerns, or problems at any time, use these contacts.**

- If you have questions about the study:  
*<< insert name and telephone number of investigator or other study staff >>*
- If your child or her baby have any health or other problems that may be related to study participation:  
*<< insert name and telephone number of investigator or other study staff >>*
- If your child wants to leave the study:  
*<< insert name and telephone number of investigator or other study staff >>*
- *<< Non-U.S. sites should modify the following as appropriate.>>* This study has been reviewed by an Institutional Review Board (IRB), a group of people that reviews human research studies. The IRB protects the rights and welfare of the people taking part in those studies. The IRB can help you if you have questions about your child's rights as a research participant or if you have other questions, concerns or complaints about this research study. If you have questions about your child or her baby's rights as research participants or concerns about how your child/her baby is being treated in the study:
  - For this multi-site study, Johns Hopkins has agreed to serve as the single IRB (sIRB) providing oversight for all sites in the U.S. You may contact the Johns Hopkins IRB at **410-502-2092** or **jhmeirb@jhmi.edu** with your questions or concerns.
  - You may also contact the [*site specific IRB contact information*] with your questions or concerns. *<< If your site wishes to include local IRB contact information, please include this here. If this is not required, please delete this section. >>*

### **Additional information about your local site:**

*<<Please insert any additional required language for your site, as applicable for this study. Examples may include*

- *Local regulatory authorities that may review study records (if different from those listed in Part 1 #17)*
- *Local language regarding state law requirements for reporting of communicable diseases or other mandated reporting requirements.*
- *Locally required language for any specific research procedures, e.g. commercialization of cell lines.*
- *Local conflict of interest disclosures*

### **How will your child's privacy be maintained and how will the confidentiality of her data be protected?**

- *Locally required HIPAA authorization language: The following language has already been approved by the JHM IRB. Please consider whether this language may be used at your site.*
  - *If this language is acceptable, it may remain in this section.*

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

- *If this language is not acceptable, and locally-approved HIPAA authorization language is required, please delete the language and replace it with your own language.*
- *Alternatively, if your site requires use of a separate HIPAA authorization, please delete this section and include the following sentence. [Add site name] requires that you sign a separate authorization form related to the use of your protected health information for this research study. This is required for participation in this study. >>*

### **HIPAA Authorization for Disclosure of Protected Health Information**

#### **What information is being collected, used, or shared?**

To do this research, we will need to collect, use, and share your child's private health information. By signing this document, you agree that your child's health care providers may release her private health information to us, and that we may use any and all of her information that the study team believes it needs to conduct the study. Your child's private information may include things learned from the procedures described in this consent form, as well as information from her medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

#### **Who will see, use or share the information?**

The people who may request, receive or use your child's private health information include the researchers and their staff. Additionally, we may share your child's information with other people at << *insert site name* >>, for example if needed for your child's clinical care or study oversight. By signing this form, you give permission to the research team to share your child's information with others outside of << *insert site name* >>. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your child's information keeps it confidential, but we cannot guarantee that your child's information will not be shared with others. If your child's information is disclosed by her health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

#### **Do you have to sign this Authorization?**

You do not have to sign this Authorization, but if you do not, your child and her baby may not join the study.

#### **How long will your information be used or shared?**

Your Authorization for the collection, use, and sharing of your child's information does not expire. Additionally, you agree that your child's information may be used for similar or related future research studies.

#### **What if you change your mind?**

You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

**Do not use this form for consenting research participants unless a stamp appears here.**

*<<US sites only.>>*

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

**Signature Lines:**

*<<US sites: If your site wishes to include site-specific signature lines, please include them here. If your site does not have site-specific signature requirements, the JHM IRB signature lines will be added in this section.*

*Non-US sites: If your site wishes to include site-specific signature lines, please include them here. If your site does not have site-specific signature requirements, please use the template lines provided below. >>*

**If you agree to allow your child to participate in this study, please sign or make your mark below.**

\_\_\_\_\_  
Name of Participant  
(print)

\_\_\_\_\_  
Name of Parent/Guardian/Legally  
Authorized Representative  
(print)

\_\_\_\_\_  
Signature of Participants

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Study Staff Conducting  
Consent Process Name (print)

\_\_\_\_\_  
Signature of Study Staff

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Witness  
(as appropriate; print)

\_\_\_\_\_  
Signature of Witness

\_\_\_\_\_  
Date

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

## **Appendix VIII: Sample Written Informed Assent Forms**

### **Appendix VIII-A: Sample Written Informed Assent Form for Participation in Component 2**

*for adolescents who cannot provide independent informed consent for study participation*

*[U.S. sites may NOT modify this assent form]*

#### **IMPAACT 2026**

### **Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum**

**Version 1.0, 22 January 2020**

#### ***Introduction***

You and your baby are being asked to take part in a research study because you are pregnant and you got at least one injection (shot) of an anti-HIV medicine called long-acting cabotegravir (CAB LA). In order for you to take part, you must give your permission. Your parent/guardian must also give their permission.

This form tells you about this study and what you will have to do if you join. Please read it, or have it read to you, and ask any questions you may have. You may have as much time as needed to fully understand the study. We will ask you questions to see if we have explained the study clearly.

#### ***Key Information***

Here is a summary of important information about the study:

- This study is to see how much of the CAB LA in a pregnant woman's body gets into her baby after the baby is born. Another purpose is to look at how safe the medicines are for mother and baby.
- If you choose to join the study and your parent/guardian agrees, you will have your first study visit before you give birth. You will also have a study visit when you have your baby.
- Your baby will be in the study for at least about two weeks after birth and will have at least three study visits.
- You will have blood drawn at each study visit after the first visit, to measure the amount of CAB LA in your blood, and your baby may have blood drawn at each visit too.
- You will be asked questions about your and your baby's health. You and your baby will have physical exams and routine blood tests.
- At select sites, women who breastfeed their baby will have breast milk collected and a couple extra study visits.
- Being in the study may not benefit you or your baby. However, this study may help doctors learn information that will help future patients who receive CAB LA injections.
- Having blood collected may cause pain, bleeding, bruising, swelling, or infection where the needle goes in your arm.

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

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- Your decision will have no effect on the medical care that you and your baby would normally receive from your clinic.

You should feel that you understand the study before deciding whether you and your baby will participate.

After you understand the study, and if you and your parent/guardian decide that you and your baby will join, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

### ***About the study***

You are already part of another study of a new medicine called CAB LA. When a woman is pregnant, medicines in her blood can get into her baby's blood. Because CAB LA is a new medicine, we don't know how much of it gets from a mother's blood into her baby during pregnancy. We don't know how long it stays in the baby's body after the baby is born. In this study, we will look at this. We will also look to see how safe these medicines are for you and your baby.

### ***Joining the study***

You and your parent/guardian will decide together if you want to join the study. If you join, you and your parent/guardian must agree for your baby to join the study too. If you and your baby join, you can change your mind later and leave the study. Your decision will have no effect on the medical care that you and your baby would normally receive from your clinic.

If you decide to join the study with your baby, we will talk to you and your parent/guardian about the study and check your medical records for information about your health, your pregnancy, and the medications that you take, to see if you qualify. We will tell you if you do or do not qualify for the study. If you qualify, you can join the study. If you do not qualify, you cannot join the study. We will also tell you when it is the right time in your pregnancy to join the study.

### ***Being in the study***

You must join the study before you have your baby. At this joining visit, we will ask you about your health and do a physical exam. We will not draw any blood at this visit.

At or near the time of delivery (when you have your baby), we will ask you questions about your health, do a physical exam, and do routine blood tests. We will collect about 13 mL (a little under 3 teaspoons) of blood to look at how much CAB LA is in your blood. Right after your baby is born, we will collect a small amount of blood from the umbilical cord. This blood does not come from your baby.

### ***Your baby's visits***

After your baby is born, your baby will be examined at least 3 times during the study: from birth to 3 days after birth, 5-9 days after birth, and 12-16 days after birth. During these visits, your baby will be weighed and measured and we will look at information about your baby's health from his/her medical records.

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

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Site Specific Consent Information Approval Date:

JHM IRB Application No.:

Your baby, if healthy enough, will have blood samples drawn at 3 times between birth and 3 days old, a fourth sample drawn between 5-9 days after birth and a fifth sample drawn at 12-16 days after birth. In these samples, we will look to see how much of the CAB LA in your blood got into your baby's blood and how long it takes to get out. We will ask you about how you feed your baby. Less than 1 mL (less than ¼ teaspoon) of blood will be collected for each sample. The total amount of blood collected from your baby for these tests will be around 4 mL (less than 1 teaspoon).

### ***Extra Visits for Some Women who Breastfeed***

Some women may choose to breastfeed their baby after their baby is born. Some women who breastfeed will have up to three extra visits to look at how much of the CAB LA in their body gets into their baby's blood through drinking breast milk. These extra visits would be within 5 weeks after giving birth.

Not all women in this study who breastfeed will have these visits. We will explain to you and your parent/guardian if you will have these visits if you breastfeed. If you do, you will have study visits with your baby at 5-9 days after birth, 12-16 days after birth, and 3-5 weeks after birth. At each of these visits, we will ask about your health, do a physical exam, weigh and measure your baby, and record information about your baby's health from her/his medical records. We will draw one 2 mL blood sample from you (less than ½ teaspoon) at each visit. For your baby, we will draw less than 1 mL (less than ¼ teaspoon) of blood at the visit at 3-5 weeks after birth. We will also collect a breast milk sample from you at each visit. Each of these extra visits for you and your baby would last about 1 hour.

### ***If you and your parent/guardian agree, some of your and your baby's blood will be used for genetic testing***

If you and your parent/guardian agree, we will use some of your and your baby's blood for genetic testing. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people break down medicines differently and this can change the levels of the medicines in their bodies. Your samples would only be used to look at differences in genes related to HIV medicines. You and your parent/guardian don't have to agree to this genetic testing. You can still join in this study even if you do not agree to genetic testing. This test will be done later in the study, so you or your parent/guardian will not receive the results. The results will not go into your medical records or have your name attached to them.

### ***Please tell us if you want to leave the study***

You and your baby are free to leave the study at any time for any reason. The care that you receive at this clinic will not be affected, but it is important for us to know about your decision.

### ***Risks of the study***

Taking part in this study may involve some risks and discomfort.

Having blood collected may cause pain, bleeding, bruising, swelling, or infection where the needle goes in your arm. Blood drawing from your baby can be done by heel stick. Heel stick may cause some discomfort, bleeding or bruising at the site of the heel stick. There is a small risk of infection at the site of the heel stick.

**Do not use this form for consenting research participants unless a stamp appears here.**

<<US sites only.>>

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

All information collected for this study will be kept private and confidential. However, it is possible that information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stressed or embarrassed.

### ***Benefits of the study***

If you take part in this study, there may be no direct benefit to you or your baby. You or your baby may benefit from having your or your baby's blood checked for safety effects. Information learned from this study may help others who receive injectable CAB in the future.

### ***Other information about the study***

Groups that oversee the study include:

- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your or your baby's name or identify you or your baby personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you or your baby. At most, the website will include a summary of the results. You can search this website at any time. If you want the results from this study, please tell the study staff.

Your or your baby's study information may be given to other authorities if required by law.

### ***What will happen with your data and specimens after the study.***

The samples collected from you and your baby will only be used for the testing described in this form. The samples will not be used for other research now or in the future. The samples will not be sold or used for commercial profit. For example, the samples will not be used to make a new product that could be sold.

Other information collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about HIV. Any future research done with the information from this study must be approved by the IMPAACT Network. If any future research is done, information about you or your baby may be used. Your or your baby's information will be labeled with a code number, and the only link between the code number and your name or your baby's name will be kept at this site. Your name or your baby's name will not be given to other researchers.

**Do not use this form for consenting research participants unless a stamp appears here.**

*<<US sites only.>>*

Lead Study Investigator:

Master Informed Consent Approval Date:

Site Specific Consent Information Approval Date:

JHM IRB Application No.:

Data or information from the study may be shared with drug companies who have agreements with the IMPAACT Network and/or the U.S. NIH, or regulatory entities, but you or your baby will never be identified personally.

**Signature Lines:**

*<<US sites: If your site wishes to include site-specific signature lines, please include them here. If your site does not have site-specific signature requirements, the JHM IRB signature lines will be added in this section.*

*Non-US sites: If your site wishes to include site-specific signature lines, please include them here. If your site does not have site-specific signature requirements, please use the template lines provided below. >>*

**If you agree to participate in this study, please sign or make your mark below.**

\_\_\_\_\_  
Name of Participant  
(print)

\_\_\_\_\_  
Signature of Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Study Staff Conducting  
Consent Process Name (print)

\_\_\_\_\_  
Signature of Study Staff

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Witness  
(as appropriate; print)

\_\_\_\_\_  
Signature of Witness

\_\_\_\_\_  
Date