



## **IMPAACT 2010**

# **Phase III Study of the Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and their Infants**

## **“VESTED”**

**Virologic Efficacy and Safety of ART  
Combinations with TAF/TDF, EFV, and DTG**

# **Manual of Procedures**

**FINAL Version 2.2  
30 January 2019**

<b>IMPAACT 2010 Manual of Procedures</b> <b>Overview of Section Contents and Identification of Current Section Versions</b>		
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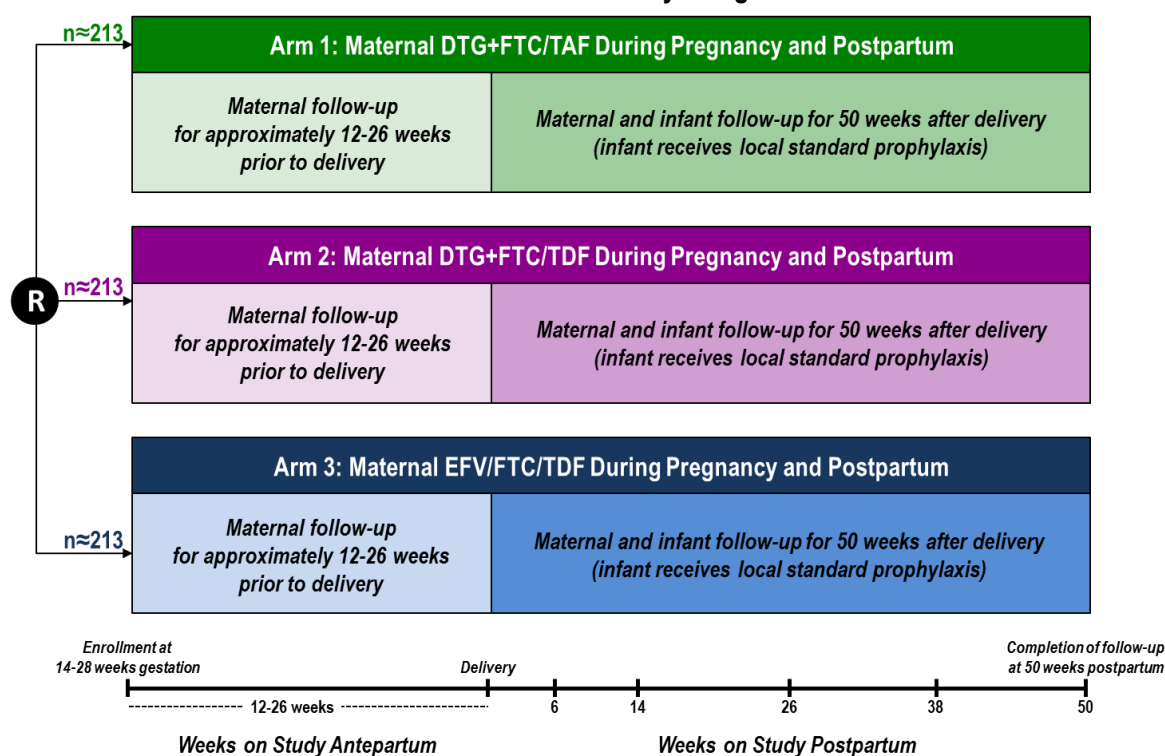
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## 1.0 STUDY OVERVIEW

IMPAACT 2010 is a Phase III, three-arm, randomized, open-label study to compare the virologic efficacy and safety of three antiretroviral regimens for HIV-1-infected pregnant women and to compare the safety of these regimens for their infants (see Figure 1-1).

Under protocol Version 2.0, 639 mother-infant pairs are planned to be enrolled in this study. Upon enrollment, mother-infant pairs will be randomly assigned to one of three study arms and mothers will receive the antiretroviral therapy (ART) regimen corresponding to their random assignment. Mothers will be followed for approximately 12-26 weeks antepartum (depending on their gestational age at enrollment); mothers and infants will be followed for 50 weeks postpartum.

**Figure 1-1**  
**IMPAACT 2010 Study Design**



On 18 May 2018 at 5:00 pm ET, accrual into the study was paused in response to new findings from the Tsepamo study indicating a potential increased risk of neural tube defects (NTDs) among infants born to mothers taking dolutegravir (DTG) at conception. Several actions were taken in response to these findings, as summarized in a “Dear Investigator” letter and associated documents issued on 15 June 2018. In addition, protocol Version 2.0 Letter of Amendment (LoA) #1, dated 20 July 2018, was issued on 27 July 2018. This LoA modified several aspects of the protocol and sample informed consent forms, including the eligibility criteria, schedule of evaluations, and considerations related to contraception and pregnancy following delivery or other outcome of the index pregnancy. Accrual into the study will be resumed, on a site-by-site basis, as required approvals of LoA #1 are obtained.

This version of the Manual of Procedures (MOP), dated 28 September 2018, reflects the specifications of protocol Version 2.0 LoA #1. Study sites should refer to this version for operational guidance upon implementation of LoA #1. Prior to implementation of LoA #1, sites should refer to prior versions of this manual.

## 2.0 PREPARING FOR THE STUDY

### 2.1 Investigator Responsibilities

IMPAACT 2010 must be conducted in accordance with the United States (US) Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice (GCP). The Division of AIDS (DAIDS) policies on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* and *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* are useful for interpreting and operationalizing the regulations and guidelines in accordance with DAIDS expectations. These policies are available at the following web site and must be followed throughout implementation of IMPAACT 2010:

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

IMPAACT 2010 also must be conducted in accordance with the IMPAACT Manual of Procedures and all site-specific regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. Copies of all applicable regulations, policies, and guidelines should be maintained in on-site essential document files. The IMPAACT Manual of Procedures is available at:

<http://impactnetwork.org/resources/policies-procedures.htm>

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

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

IoRs may delegate their obligations and responsibilities for conducting IMPAACT 2010 to other study staff; however, delegation does not relieve the IoR of his or her ultimate responsibility for all study procedures performed and all study data collected. Delegation of IoR responsibilities must be formally documented throughout the period of study implementation.

Consistent with the regulations, guidelines, and policies cited above, the IoR at each site must obtain all applicable drug regulatory and ethical review approvals for IMPAACT 2010 prior to study initiation; the IoR must also maintain these approvals in good standing throughout the period of study implementation. With regard to drug regulatory authorities (DRAs), the IoR must complete initial and continuing submissions in accordance with DRA policies. With regard to institutional review boards and ethics committees (IRBs/ECs), further guidance on initial and continuing review requirements is available in 45 CFR 46 and the ICH GCP guidance, as well as on the web site of the US Office for Human Research Protections (OHRP):

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

All sites are encouraged to request an acknowledgement of receipt for all documents submitted to their DRAs and IRBs/ECs and to request that DRAs and IRBs/ECs note the effective and expiry dates of all approvals. Because IMPAACT 2010 involves pregnant women, fetuses, and infants, IRBs/ECs must consider the potential risks and benefits of the study for mothers and children as described in protocol Section 12.2. Complete documentation of all correspondence to and from all responsible DRAs and IRBs/ECs (i.e., complete copies of all submissions, responses, and approvals) must be maintained in on-site essential document files. All submission letters should list the date of the submission, the contents of the submission, and the version number and/or version date of each document submitted.

## 2.2 Protocol Registration

After obtaining all required DRA and IRB/EC approvals, each participating study site is responsible for submitting documentation of the approvals, and other required documents, to the DAIDS Protocol Registration Office (PRO). Further information on the protocol registration process can be found in protocol Section 13.2 and in the *DAIDS Protocol Registration Manual*, which is available at:

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

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

## 2.3 Site-Specific Study Activation

Prior to conducting any study procedures, each site must obtain all required approvals (as described above) and must complete study activation procedures with the Protocol Team. To help ensure site readiness for study initiation, the Protocol Team has specified a set of study activation requirements that must be met in order to obtain approval to begin study implementation. These requirements are listed on the IMPAACT 2010 Site-Specific Study Activation Checklist, which is available upon request from the IMPAACT Operations Center Clinical Trial Specialists.

- Sites that completed the DAIDS protocol registration process for protocol Version 1.0 prior to distribution of protocol Version 2.0 were permitted to initiate the study under protocol Version 1.0, once all study activation requirements were met. For these sites, it was not necessary to obtain approval of protocol Version 2.0 prior to study activation. *Note:* as of 18 July 2018, all of these sites had transitioned to study implementation under protocol Version 2.0.
- Sites that did not complete the DAIDS protocol registration process for protocol Version 1.0 prior to distribution of protocol Version 2.0 were not permitted — per DAIDS policies — to initiate the study under protocol Version 1.0. These sites must obtain approval and complete the DAIDS protocol registration process for protocol Version 2.0 and LoA #1 and complete all other study activation requirements prior to study activation.

Any questions related to the study activation process should be directed to the IMPAACT Operations Center Clinical Trial Specialists. On a site-by-site basis, when all activation requirements have been met, the Operations Center will issue a Site-Specific Study Activation Notice. At each site, no study procedures may be conducted prior to receipt of an activation notice.

## 3.0 STUDY-RELATED INFORMATION AND COMMUNICATIONS

All IMPAACT 2010 visits and procedures must be conducted in accordance with the study protocol. The purpose of this manual is to supplement the protocol, not to replace or substitute for it. In the event that this manual is inconsistent with the protocol, the specifications of the protocol take precedence. Please notify the IMPAACT Operations Center Clinical Trial Specialists of any such inconsistencies.

The IMPAACT 2010 protocol and related protocol documents are available on the study-specific web page:

<http://impaactnetwork.org/studies/IMPAACT2010.asp>

The Protocol Team has identified study-specific contacts for various types of issues and questions, as shown in Figure 3-1. For issues and questions directed to members of the Protocol Team (e.g., the Questions Group or Clinical Management Committee (CMC)), a response from the appropriate team member can generally be expected within 24 hours.

Figure 3-2 lists the study-specific email groups that have been created for IMPAACT 2010. With the exception of the protocol email group ([IMPAACT.prot2010@fstrf.org](mailto:IMPAACT.prot2010@fstrf.org)), these groups are maintained by the Operations Center Clinical Trial Specialists; please contact the Clinical Trial Specialists to request changes or updates for these groups. For the protocol email group, contact [user.support@fstrf.org](mailto:user.support@fstrf.org).

Site staff should avoid sending messages to the protocol email group ([IMPAACT.prot2010@fstrf.org](mailto:IMPAACT.prot2010@fstrf.org)) as this group is used for broadcast distribution to all Protocol Team members and study sites. The group is comprised of hundreds of individuals and is not intended to receive site-specific or participant-specific queries. Questions related to interpretation of the protocol or participant management should generally be emailed to the IMPAACT 2010 Questions Group ([IMPAACT.2010questions@fstrf.org](mailto:IMPAACT.2010questions@fstrf.org)) or the CMC ([IMPAACT.2010CMC@fstrf.org](mailto:IMPAACT.2010CMC@fstrf.org)).

As indicated in Figure 3-3, active communication is expected between site staff and the CMC. When submitting questions and notifications to the CMC, to help ensure that CMC members have adequate information to respond in a timely manner, please address each of the points listed in Figure 3-3. Always retain a copy of correspondence with the CMC in the relevant participant's study chart.



**Figure 3-1**  
**IMPAACT 2010 Study-Related Communications**

Topic	Contact
Adding site staff to protocol email group ( <a href="mailto:IMPAACT.prot2010@fstrf.org">IMPAACT.prot2010@fstrf.org</a> )	<b>User Support</b> <a href="mailto:user.support@fstrf.org">user.support@fstrf.org</a> (include the protocol number in the subject line of your email message)
Any aspect of protocol interpretation or study implementation not listed below	<b>IMPAACT 2010 Questions Group</b> <a href="mailto:IMPAACT.2010questions@fstrf.org">IMPAACT.2010questions@fstrf.org</a> (for triage to other team members as needed)
Clinical, adverse event, and study drug management issues	<b>IMPAACT 2010 Clinical Management Committee</b> <a href="mailto:IMPAACT.2010CMC@fstrf.org">IMPAACT.2010CMC@fstrf.org</a>
Participant eligibility, potential enrollment of an ineligible participant, and/or deviation from protocol requirements for eligibility determination and/or enrollment	<b>IMPAACT 2010 Clinical Management Committee</b> <a href="mailto:IMPAACT.2010CMC@fstrf.org">IMPAACT.2010CMC@fstrf.org</a>
Co-enrollment issues	<b>IMPAACT 2010 Clinical Management Committee</b> <a href="mailto:IMPAACT.2010CMC@fstrf.org">IMPAACT.2010CMC@fstrf.org</a>
Data management computer and screen problems	<b>User Support</b> <a href="mailto:user.support@fstrf.org">user.support@fstrf.org</a> (or by phone: +716-834-0900 x7302)
Subject Enrollment System	<b>DMC Randomization Support Office</b> <a href="mailto:rando.support@fstrf.org">rando.support@fstrf.org</a> (or by phone: +716-834-0900 x7301)
Study drug issues (other than study drug orders)	<b>Protocol Pharmacist</b> <a href="mailto:lpurdue@niaid.nih.gov">lpurdue@niaid.nih.gov</a> or by phone: +240-627-3061
Study drug orders	<b>Clinical Research Products Management Center</b> <a href="mailto:BIO.CRPMC.Ph@Thermofisher.com">BIO.CRPMC.Ph@Thermofisher.com</a> (or by phone: +301-294-0741)

**Figure 3-2**  
**IMPAACT 2010 Email Groups**

Email Group	Membership
<a href="mailto:IMPAACT.team2010@fstrf.org">IMPAACT.team2010@fstrf.org</a>	Individuals listed in the Protocol Team Roster of the protocol
<a href="mailto:IMPAACT.team2010investigators@fstrf.org">IMPAACT.team2010investigators@fstrf.org</a>	Site investigators (and designees) listed in the Site Representatives Roster of the protocol
<a href="mailto:IMPAACT.team2010coordinators@fstrf.org">IMPAACT.team2010coordinators@fstrf.org</a>	Site coordinators (and designees) listed in the Site Representatives Roster of the protocol
<a href="mailto:IMPAACT.2010pharm@fstrf.org">IMPAACT.2010pharm@fstrf.org</a>	Site Pharmacists of Record, Site Back-Up Pharmacists, and Protocol Pharmacist
<a href="mailto:IMPAACT.prot2010@fstrf.org">IMPAACT.prot2010@fstrf.org</a>	All team and site representatives (also includes all other study-specific groups)

**Figure 3-3**  
**Communications with IMPAACT 2010 Clinical Management Committee**

**Questions and notifications for IMPAACT 2010 CMC: Copy and paste this listing into the body of your email message to [impaact.2010CMC@fstrf.org](mailto:impaact.2010CMC@fstrf.org) to help ensure that all required information is included.**

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

1. Site number
2. Name of person submitting query
3. Participant type (mother or infant)
4. PID
5. Reason for query (choose one):
  - a. Consultation on eligibility or enrollment (describe in case description)
  - b. Consultation on adverse event or toxicity management (describe in case description)
  - c. Consultation on study drug management (describe in case description)
  - d. Other (specify in case description)
6. Age of participant
7. Current week on study
8. *For maternal queries:* currently pregnant?
9. *For maternal queries:* co-infected with hepatitis B?
10. *For maternal queries:* current ARV regimen?
11. *For mother and infant queries:* currently breastfeeding?
12. *For infant queries:* sex, HIV status, ARV regimen (prophylaxis or treatment, current or prior)
13. Case description and question or notification for CMC

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

## 4.0 PARTICIPANT ACCRUAL

### 4.1 Overview

Under protocol Version 2.0, 639 mother-infant pairs are targeted to be enrolled in this study.

### 4.2 Site-Specific Accrual

The study accrual plan is based on site-specific accrual projections established during the site selection process, with updates in the first half of 2017 and the first quarter of 2018. Across sites, accrual was originally expected to be completed within 12 months; however, due to the accrual pause that began on 18 May 2018, the accrual period will be extended.

For each site, accrual will begin after all required approvals are obtained and a site-specific study activation notice is issued by the IMPAACT Operations Center. As a condition for study activation, each site will establish SOPs for participant accrual. All sites are responsible for following these SOPs, and for updating them if needed to meet their pre-specified accrual projections, throughout the study accrual period.

Additional considerations related to resuming accrual following the pause that began on 18 May 2018 — consistent with the Information/Instructions to Study Sites from the Division of AIDS on page 2 of LoA #1 — are provided in the table below.

For sites activated before LoA #1 was issued
<ul style="list-style-type: none"><li>LoA #1 should be implemented immediately upon receipt of the Implementation Notice for the LoA <u>and</u> receipt of all required IRB/EC and regulatory entity approvals of the LoA. Implementation should <u>not</u> await protocol registration for the LoA.</li><li>Upon receipt of all required approvals of the LoA, notify the IMPAACT Operations Center. This will assist with tracking LoA implementation dates across sites and will enable re-opening of screening and enrolment screens in the Subject Enrollment System. Any delay in notifying the Operations Center will result in a delay in opening the screens, thereby delaying the resumption of accrual at the site.</li><li>Beginning on the LoA implementation date at each site, all study visits and procedures should be conducted per the specifications of the LoA.<ul style="list-style-type: none"><li>For previously enrolled participants, re-consent for study participation should be obtained at the next scheduled visit using site-specific ICFs that correspond to the LoA.</li><li>For newly screened and enrolled participants, informed consent for study participation should be obtained using site-specific ICFs that correspond to the LoA.</li></ul></li></ul>
For sites <u>not</u> activated before LoA #1 was issued
<ul style="list-style-type: none"><li>LoA #1 will be implemented upon activation to initiate the study (i.e., study implementation will be initiated under protocol Version 2.0 and LoA #1).</li><li>Activation will occur when all the following requirements have been met:<ul style="list-style-type: none"><li>The Implementation Notice for LoA #1 has been issued.</li><li>All required IRB/EC and regulatory entity approvals and a protocol registration notice have been obtained for protocol Version 2.0.</li><li>All required IRB/EC and regulatory entity approvals and a protocol registration notice for LoA #1.</li><li>All other study activation requirements have been completed.</li><li>A site-specific study activation notice from the IMPAACT Operations Center.</li></ul></li><li>For newly screened and enrolled participants, informed consent for study participation should be obtained using site-specific ICFs corresponding to the LoA.</li></ul>

The Statistical and Data Management Center (SDMC) will routinely report the number of mother-infant pairs screened and enrolled at each site — by month and cumulatively — to the Protocol Team; monthly and cumulative data on the screen-to-enroll ratio will also be reported to the team. The team will monitor these data in relation to site-specific accrual projections to determine whether accrual targets should be adjusted across sites to achieve the study objectives most efficiently and to determine when to discontinue accrual at each site. Findings and recommendations from these reviews will be communicated to all sites, and all sites will adjust their accrual efforts accordingly. Similar adjustments may be made in response to DSMB reviews of the study.

### 4.3 Participant Recruitment, Screening, and Enrollment

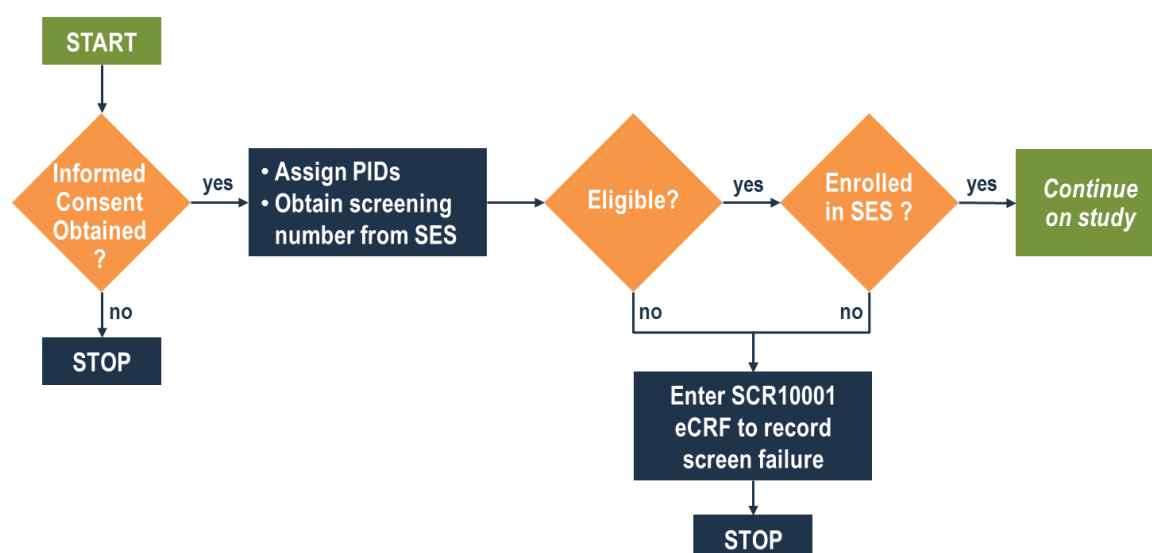
Refer to protocol Section 4.4 for an overview of the participant recruitment, screening, and enrollment process for this study. Participant recruitment methods may vary across sites but are expected to rely on active identification and referral of HIV-1-infected pregnant women who are not taking ART at the time of presenting for antenatal care. Based on current standards of care, it is expected that many such women will be started on a non-study ART regimen at the time of presenting for antenatal care. This is permitted (but not required) by the study eligibility criteria. However, recruitment and eligibility screening procedures will need to be performed in a timely manner to ensure that eligible women are enrolled within 14 days of starting non-study ART.

While recruitment methods may vary across sites, screening and enrollment methods will be more standardized across sites, consistent with the requirements of protocol Sections 6.1 and 6.2.

A schematic overview of the recruitment, screening, and enrollment process is provided in Figure 4-1; selected operational considerations related to this process are described in the remainder of this section. To minimize the number of days on non-study ART prior to enrollment, sites are encouraged to complete the study screening and enrollment process as rapidly as possible following identification of a potentially eligible mother-infant pair.

*Note:* It is theoretically possible for screening and enrollment to occur on the same day, and this is permitted per protocol. However, all required screening findings — including screening laboratory test results — must be available for eligibility determination prior to enrollment.

**Figure 4-1**  
**IMPAACT 2010 Recruitment, Screening, and Enrollment Process**



### 4.3.1 Obtaining Informed Consent

Refer to Section 5 of this manual for detailed guidance on obtaining informed consent for this study. Written informed consent for maternal and infant study participation must be obtained before any study-specific procedures are performed.

### 4.3.2 Assigning Participant Identification Numbers

A participant identification (PID) number must be assigned to each potential participant — mother and infant — for whom informed consent for study participation is obtained. The only exception to this requirement applies when a participant has previously been assigned a PID for another IMPAACT or ACTG study. In that case, the previously-assigned PID would be used for IMPAACT 2010.

Study site staff should assign PIDs from lists provided by the DMC. Sites may choose (but are not required) to use lists of PIDs that visually link maternal and infant PIDs. Contact the DMC with any questions related to use of PID lists.

### 4.3.3 Screening for Eligibility

The study eligibility criteria are provided in protocol Sections 4.1 and 4.2; procedural eligibility screening requirements are described in protocol Section 6.1 (Screening Visit) and 6.2 (Entry Visit).

*Note:* Inclusion criterion 4.1.6 requires a gestational age of 14-28 weeks at study entry. Please refer to the appendix at the end of this section (starting on page 28) for guidance on determining gestational age for purposes of eligibility determination.

*Note:* Inclusion criterion 4.1.2 requires confirmation of maternal HIV-1 infection prior to study entry and exclusion criterion 4.2.4 requires exclusion of mothers with a history of HIV-2 infection. As communicated to study sites via email on 8 May 2018, and as clarified in LoA #1, all sites must include at least one test in their maternal HIV testing algorithm that can distinguish HIV-1 from HIV-2. This is also addressed in FAQ 4-Q and Section Appendix 4-2.

*Note:* Inclusion criterion 4.1.8 was added in LoA #1. This criterion requires that mothers do not wish to become pregnant again for at least 50 weeks after the current pregnancy and are willing to use effective contraception during this period. All mothers enrolled following resumption of accrual under LoA #1 must meet this criterion.

As described in Section 4.3.2, a PID will be assigned to all potential participants for whom informed consent for study participation is obtained. In addition, a study-specific screening number will be obtained for each mother-infant pair through the DMC's Subject Enrollment System (SES). Pairs who are found meet all eligibility criteria will be enrolled in the study using the SES. For pairs who are found to be ineligible, or who do not enroll in the study for any reason, the SCR10001 eCRF must be entered to record the screening outcome.

It is the responsibility of the IoR and other designated study staff to ensure that all required screening procedures are performed and adequately documented, and that only mother-infant pairs who meet the study eligibility criteria are enrolled. Each site must have on file a study-specific SOP for eligibility determination that describes how study staff will fulfill this responsibility; all sites must follow their SOPs when assessing eligibility for all potential participants. ***In the event that study staff identify that an ineligible participant has been enrolled, the CMC must be consulted as soon as possible and within no more than 24 hours*** per the communication procedures described in Section 3 of this manual.

#### 4.3.4 FAQs Related to Eligibility

- 4-A The study eligibility criteria allow for enrollment of women who are 14-28 weeks pregnant at study entry. Fourteen weeks is defined as greater than 13 weeks plus six days, but “less than 28 completed weeks” is not similarly defined. How should we operationalize this?**

For purposes of inclusion in this study, less than 28 completed weeks is defined as up to 27 weeks plus six days.

- 4-B The eligibility criteria allow for women to have received ARVs during prior pregnancies or period of breastfeeding; should we be concerned about NNRTI resistance in this setting? Will we be able to perform genotypic resistance testing if resistance is suspected?**

We anticipate that a reasonable proportion of women will have taken an NNRTI during one or more previous pregnancies (including single dose nevirapine), and that a subset of these women may have archived (or even detectable) NNRTI-resistant virus. However, we decided that we would not exclude women with prior NNRTI exposure during pregnancy/breastfeeding for two main reasons:

- a. We want our study findings to be relevant and generalizable to the population of pregnant women who are accessing ART/PMTCT in current real-world settings. Restricting the study to women without any prior NNRTI exposure for PMTCT would limit the generalizability of study findings.
- b. It is very challenging (often impossible) to reliably ascertain prior NNRTI exposure (or lack thereof) among participants in most of the study sites. In particular, documentation and recall of single dose nevirapine ingestion (which arguably poses the greatest risk for selecting for NNRTI-resistant virus) is notoriously poor.

We plan to perform ARV drug resistance testing for mothers who experience confirmed virologic failure; if resistance is present at the time of failure, then resistance testing will also be performed on baseline samples (collected at screening).

- 4-C The eligibility criteria allow for women to receive up to 14 days of ART during their current pregnancy, prior to enrollment. If a woman has not received any ARVs during her current pregnancy, can she enroll in the study?**

Yes. There are no eligibility criteria that require receipt of ARVs prior to study entry. As part of the informed consent process, however, study staff should confirm each woman's willingness to take ARVs (based on the study group to which she is assigned) upon enrollment in the study.

- 4-D The eligibility criteria allow for women to receive up to 14 days of ART during their current pregnancy, prior to enrollment. If a woman received DTG or TAF as part of her pre-study ART regimen (prior to enrollment), can she enroll in the study?**

Yes. Use of any ARV is permitted during the current pregnancy, prior to enrollment.

As noted above, as part of the informed consent process, study staff should confirm each woman's willingness to take ARVs based on the study group to which she is assigned. If a woman is not willing to switch from her pre-study regimen to whatever regimen she is assigned to for the study, she should not be enrolled in the study.

**4-E** We understand that a woman can receive up to 14 days of ART during her current pregnancy prior to enrollment. If, on the day of screening, a woman has received 12 days of ART during her current pregnancy, can we advise her to stop taking ARVs to allow more time to complete the screening process?

No. Once a woman has started ART in her current pregnancy, we would not want study-specific requirements to interfere with current standards of care which specify uninterrupted ART from the date of initiation.

**4-F** We would like to ask for clarification of the 14 days of ART that are permitted during the current pregnancy prior to enrollment. Inclusion criterion 4.1.3 allows for receipt of up to 14 days of ARVs during the current pregnancy prior to study entry, and the note below this criterion states that enrollment must occur within 14 days of ART initiation. We are trying to think through these requirements in relation to women who may miss some doses of ART in the current pregnancy (before enrollment). For example, if a woman started ART for a few days, then missed a few days, and then started again, how should we count that in relation to eligibility for the study?

Your question correctly highlights that the wording of the note below Inclusion Criterion 4.1.3, which is also used in other sections of the protocol, is somewhat more restrictive than the wording of the criterion itself. For women who do not miss any doses of ART during the current pregnancy, there will be no discrepancies based on the wording of the criterion and the wording of the note. For women who do miss doses of ART during the current pregnancy, there could be a discrepancy, and it will be necessary to assess eligibility based on the more restrictive wording of the note.

For example, if a woman initiated ART on 1 August 2017 and then took ART consistently with no missed doses, she would need to be enrolled by 14 August 2017. That date is “within 14 days of ART initiation” and, as of that date, the woman would have received ART on 14 days.

As another example, consider a woman who initiated ART on 1 August 2017 and took her regimen for three days, then missed on two days, but did not miss any doses after that. This woman would still need to be enrolled in the study “within 14 days of ART initiation,” which would be by 14 August 2017. In this case, 14 August 2017 would be the last possible day to enroll even though the woman would have only received ART on 12 days as of this date. This example highlights that the more restrictive wording of the note, which requires enrollment within 14 days of ART initiation, must be followed for women who miss doses of ART prior to enrollment.

**4-G** We would like to ask about a scenario in which a woman lost a pregnancy in the past. If this woman took ART during that pregnancy, and then stopped taking ART when the pregnancy was lost, would she be eligible for the study?

Yes. Because this mother’s prior use of ART was time-limited within a prior period of pregnancy, she would be potentially eligible for IMPAACT 2010.



**4-H We would like to ask about a scenario in which a woman took ART during a prior pregnancy. After birth, the baby was formula fed, and the woman stopped taking her ART due to problems with adherence. Would this mother be eligible for the study?**

The answer to this question would likely depend on the specific details of when the woman started taking ART and when she stopped, in relation to her prior pregnancy. The team would recommend that you contact the CMC to review these details and confirm whether the woman may be eligible for the study. In general, however, only time-limited periods of ART use during prior periods of pregnancy and breastfeeding would be considered allowable.

**4-I Under protocol Version 2.0, eligibility criterion 4.2.4 excludes women who have received "any antiretroviral medication within six months prior to study entry, with two exceptions: receipt of any duration of TDF or FTC/TDF for pre-exposure prophylaxis or receipt up 14 days of ARVs during the current pregnancy." We would like to confirm our understanding of this change. Does this mean that women who received TDF or FTC/TDF for PrEP while HIV-negative, who screen for the study after becoming HIV-positive, can be enrolled even if the PrEP was taken within six months prior to study entry?**

Yes. Eligibility criterion 4.2.4 was revised in protocol Version 2.0 to allow any use of TDF or FTC/TDF for PrEP. Therefore, use of these ARVs for PrEP, even in the six months prior to study entry, is not exclusionary under protocol Version 2.0.

**4-J The eligibility criteria seem to allow for women with hepatitis B or hepatitis C to take part in the study. Are there any clinical management issues or concerns that we should be aware of for these women, particularly with respect to initiation of DTG or TAF?**

The protocol does not require laboratory testing for hepatitis B or hepatitis C infection as part of the study screening process, although hepatitis B testing is required at entry. You are correct that these infections are not exclusionary; however, grade 2 or higher ALT and AST values are exclusionary, as is current treatment for active hepatitis C. Unstable liver disease within 14 days prior to study entry is also exclusionary. For enrolled mothers who are not receiving treatment for active hepatitis C at study entry, but who may later receive such treatment during follow-up, the CMC should be consulted with respect to the potential use of precautionary or prohibited concomitant medications (refer to protocol Sections 5.9 and 5.10).

TDF, TAF, and FTC have antiviral activity against hepatitis B. These ARVs as well as DTG have been used successfully in ART regimens for HIV-infected patients with hepatitis B and hepatitis C. EFV has also been used successfully in HIV-infected patients with hepatitis; however, an association with severe drug-induced liver injury (DILI) has been reported for EFV, with higher CD4 count at ART initiation, younger age, and possibly female gender associated with these DILI events (see protocol reference [4]).

Individuals with hepatitis B co-infection may experience transient worsening of hepatitis symptoms after stopping TDF, TAF, or FTC (or after first initiating ARV regimens that include these drugs). In IMPAACT 2010, per the Schedule of Evaluations, mothers with hepatitis B or hepatitis C are generally expected to be monitored in the same manner as mothers who do not have these infections. Protocol Section 8.5 provides management guidance for mothers with hepatitis B infection. Tables II.3 and II.4 in Appendix II provide detailed instructions for management of asymptomatic elevated ALT and AST values and symptomatic hepatitis, respectively.



**4-K** We are not sure if the documentation of HIV testing typically available from local antenatal clinics will meet protocol criteria as adequate for confirmation of maternal HIV infection. For example, two rapid tests are performed per Ministry of Health guidelines, and which tests are stocked in the clinics, but the result slips completed in the clinics do not state the names of the test kits. Can we use this documentation for study purposes?

The answer to this question may depend on the totality of documentation available to you. For example, if there are Ministry of Health policy or procedural documents that specify which tests are used, it may be possible to combine these documents with the result slips as a package that would be considered adequate documentation. Please provide copies of the documentation that is available to you to the Clinical Trials Specialists; following review of this documentation, the team will provide further guidance on acceptable options for your site.

**4-L** The protocol states that fetal ultrasound should be performed if possible during the study screening period, or otherwise within 14 days after study entry. If an ultrasound scan was performed prior to the study screening period, and adequate documentation of the scan results are available, can we use this scan for study purposes, or do we need to perform another scan within 14 days prior to study entry?

This issue was first addressed in protocol Version 1.0 Clarification Memorandum #2, the content of which was incorporated into protocol Version 2.0. Ultrasound scans performed prior to the study screening period may be used for study purposes, provided the result reports from such scans meet the minimum requirements specified in protocol Section 6.13. This is an exception to the protocol specification that screening procedures must be performed within 14 days prior to enrollment. When a prior ultrasound scan result report that meets protocol requirements is available, it is not necessary to perform an additional scan for study purposes. When more than one ultrasound result report that meets protocol requirements is available, the earliest available results should be entered into eCRFs for estimation of gestational age.

**4-M** We would like to ask about a scenario during screening in which gestational age assessed by LMP or other clinical assessment differs from gestational age assessed by ultrasound, and one of the assessments provides an exclusionary result. Should the ultrasound result always be used for eligibility determination, or is there other guidance that should be followed?

Please refer to the appendix at the end of this section and contact the CMC with any questions related to eligibility based on gestational age.

**4-N** In the event that a fetal ultrasound scan cannot be performed prior to study entry, should we always use the same clinical method to estimate gestational age, or can the method used vary from woman to woman? We have taken note that the protocol states that "the best available method" should be used.

In the expected rare event that ultrasound cannot be performed prior to study entry, estimation from date of last menstrual period (LMP) is generally the next most reliable method, for women who can recall their LMP with reasonable confidence. Please contact the CMC to discuss any situation in which the best method to use is unclear.

**4-O In the event that a fetal ultrasound scan is performed after enrollment, and identifies that the woman is pregnant with twins, or that the fetus has a congenital anomaly, or that the gestational age is outside of the allowable range, does the woman need to be discontinued from the study?**

Per protocol Section 6.1, “Participants will not be withdrawn from the study if ultrasound performed after entry identifies an exclusionary condition (i.e., multiple gestation, fetal anomaly, or gestational age outside of the allowable range of 14-28 weeks).” Likewise, protocol Section 6.13 states, “When scans are performed after study entry, any findings that indicate multiple gestation, fetal anomaly, or gestational age outside of the allowable range of 14-28 weeks will be recorded but will not be considered eligibility violations and will not result in withdrawal from the study.”

The protocol specifies that potential participants with known multiple gestations and fetal anomalies should be excluded from the study to minimize the occurrence of pregnancy outcomes that are likely to complicate the interpretation of study results. However, if these participants are not excluded prior to study entry, there is no specific safety concern associated with use of the study drug regimens by these participants. Thus, there is no *a priori* reason to withdraw these participants from the study.

**4-P We would like to ask about a situation in which an enrolled mother undergoes one or more fetal ultrasounds before the birth of her baby. Let’s say the first ultrasound, which was performed prior to enrollment, did not identify any congenital anomalies. Then a second or third ultrasound, performed after enrollment, identifies something new, an anomaly that was not seen before. Would we document that anomaly as a pre-existing condition or as an adverse event for the infant?**

The anomaly should be documented as an adverse event for the infant.

In this case, the fetal ultrasound report that identifies the anomaly would be filed in the infant’s study chart as source documentation. When the infant is born, he or she would be examined by a study clinician per protocol and the ultrasound report and physical examination findings would be considered together to determine all of the adverse events that should be entered into the Adverse Event Log eCRF for the infant. If a congenital anomaly is diagnosed, additional eCRF entries (into the DXW10000 eCRF) and expedited adverse event reporting would also be required. Should you have any questions about how to report any ultrasound or physical examination findings for any infant, please contact the CMC.

**4-Q We have noted that protocol Version 2.0 has a new exclusion criterion for maternal HIV-2 infection. Does this mean we must test for HIV-2 at screening?**

No, it is not necessary to test for HIV-2 to assess for this exclusion criterion. Rather, this criterion should be assessed based on the mother's reported medical history and available medical records.

When considering this question, it is also important to consider inclusion criterion 4.1.2, which specifies requirements for confirmation of maternal HIV-1 infection. As stated in an email message from the Protocol Team dated 8 May 2018, all sites must include at least one test that can distinguish HIV-1 from HIV-2 in their HIV testing algorithm for this study. Tests that meet the requirements of inclusion criterion 4.1.2, and that can distinguish HIV-1 from HIV-2, include the Geenius™ HIV 1/2 Supplemental Assay, Bio-Rad Western blot, and HIV-1 RNA PCR assays. It is acceptable to use HIV 1/2 antibody tests for Sample #1, provided that a test that can distinguish HIV-1 from HIV-2 is used for Sample #2. Clarifications related to these requirements were added to the protocol in LoA #1.

**4-R In our setting, it is common for ART initiation to be deferred pending resistance testing. Therefore, we expect resistance test results to be available in medical records for at least some of the women who we screen for the study. How should we consider these results when deciding whether to enroll a woman in the study?**

Resistance testing is not required prior to study entry. However, an exclusion was added to criterion 4.2.4 in protocol Version 2.0 for “antiretroviral drug resistance mutations that would impact selection of ART regimen (ever).” Therefore, if resistance test results are available prior to study entry, these must be considered when assessing eligibility and making enrollment decisions. If a woman has documented resistance to one or more of the study drugs, consultation with the CMC is strongly encouraged, as participation in the study — with random assignment to one of the study drug regimens — may not be in the best interest of the woman, in which case exclusion from the study would be expected per criterion 4.2.4.

**4-S In our setting, the standard of care for initiation of ART involves sending a sample for ARV resistance testing. However, the results of this testing are not usually received until 6-8 weeks later. How should we handle this for women who are screened for VESTED?**

The Protocol Team recommends that your standard of care be followed.

- If resistance test results are received prior to enrollment, these should be handled consistent with FAQ 4-R (above).
- If resistance test results are received after enrollment, and resistance to one or more of the study drugs is identified, please consult with the CMC as soon as possible after the result is obtained to discuss options for ARV regimen management.

**4-T We understand that the Edinburgh Postnatal Depression Scale (EPDS) is administered at Weeks 6 and 50 Postpartum per the Schedule of Evaluations. For purposes of baseline assessment and eligibility determination — to rule out suicidal ideation or attempt — can we administer the EPDS at screening?**

The EPDS should not be administered at screening, for two reasons. First, the EPDS was designed to assess for indicators of postpartum depression; therefore, its usefulness during pregnancy, for the purposes identified in your question, is uncertain. Second, the EPDS is not intended to be — and should not be — used for diagnostic purposes in this study. Instead of using the EPDS at screening, the Protocol Team recommends that each site develop targeted baseline medical history questions that can be translated into local languages and used routinely at screening visits for purposes of baseline assessment and eligibility determination.

**4-U We would like to clarify the part of exclusion criterion 4.2.4 that would exclude mothers with a “clinically significant acute illness requiring systemic treatment and/or hospitalization within 14 days prior to study entry.” In our setting, pregnant women are often presumptively treated with antibiotics for vaginal discharge and/or sexually transmitted infections. We also expect to see women with respiratory tract infections that may be treated with antibiotics. Would these women need to be excluded from the study due to the systemic treatment received?**

For purposes of eligibility determination in relation to this criterion, both the condition being treated and the treatment given should be considered. The intent of this criterion is to exclude women with major medical conditions that are likely to lead to hospitalization and/or an adverse pregnancy outcome, as was clarified in LoA #1. Such conditions may include pneumonia or a new diagnosis of tuberculosis, for example. Conditions such as uncomplicated sexually transmitted infections, urinary tract infection, upper respiratory tract infection, bronchitis, or mild gastroenteritis would not generally be considered exclusionary. If you have further questions about this or would like further guidance for an individual mother being screened for the study, please contact the CMC.

**4-V We would like to clarify the part of inclusion criterion 4.1.3 and exclusion criterion 4.2.4 that involve maternal receipt of ARVs prior to study entry. These criteria address antiretroviral therapy and pre-exposure prophylaxis but we now have a question about post-exposure prophylaxis (PEP); would mothers who have received PEP need to be excluded from the study?**

In relation to criterion 4.1.3, prior receipt of ARVs for PEP would not be exclusionary, because PEP does not constitute antiretroviral therapy. In relation to criterion 4.2.4, the timing of when a mother received PEP would need to be considered. ARVs received for PEP within six months prior to study entry would be exclusionary; ARVs received for PEP more than six months prior to entry would not.

If you have further questions about this or would like further guidance for an individual mother being screened for the study, please contact the CMC.

#### **4.3.5 Enrolling Eligible Participants**

Mother-infant pairs will be considered enrolled in this study upon successful entry of eligibility checklist data into the SES, which will result in generation of Study ID Numbers (SIDs) for the mother and infant and random assignment to one of the three study arms. Examples of SES confirmation files, which provide SIDs for this study, are provided in Figure 4-2 (on pages 24-26).

Refer to protocol Section 6.2 for Entry Visit requirements, including requirements related to the timing and ordering of Entry Visit procedures, which should be taken into consideration when planning for logistical and staffing needs for these visits. Further information of the timing of enrollment, vis-à-vis the study eligibility criteria, is provided in the examples below. Please contact the CMC with any questions involving interpretation of these timelines for any mother-infant pair.

**Example #1:** In this example, the mother presents for antenatal care and is found to be HIV-positive on the 1st of the month. She is given the local standard ART regimen and takes her first dose of ART that same day. Two days later, on the 3rd of the month, she reports to the study clinic, provides informed consent, and undergoes screening evaluations.

SUN	MON	TUE	WED	THU	FRI	SAT
		1 Starts ART	2	3 Starts Screening	4	5
6	7	8	9	10	11	12
13	14 Last day to enroll	15	16	17	18	19
20	21	22	23	24	25	26

All screening evaluations must be performed within 14 days of enrollment, and enrollment must occur within 14 days of (non-study) ART initiation during the current pregnancy. In this example, ART was started before screening evaluations were performed, so the date of ART initiation determines the last possible day for the mother-infant pair to be enrolled, which is the 14th of the month.

**Example #2:** In this example, the mother presents for antenatal care and is found to be HIV-positive on the 1st of the month. She is given the local standard ART regimen that day but does not start taking the medication that day. Two days later, on the 3rd of the month, she reports to the study clinic, provides informed consent, and undergoes screening evaluations. Following counseling received from study staff, she takes her first dose of non-study ART on the 4th of the month.

SUN	MON	TUE	WED	THU	FRI	SAT
		1	2	3 Starts Screening	4 Starts ART	5
6	7	8	9	10	11	12
13	14	15	16 Last day to enroll	17	18	19
20	21	22	23	24	25	26

All screening evaluations must be performed within 14 days of enrollment, and enrollment must occur within 14 days of (non-study) ART initiation during the current pregnancy. In this example, screening evaluations were performed before ART was initiated, so the screening visit date determines the last possible day to enroll, which is the 16th of the month.

**Example #3:** In this example, the mother presents for antenatal care and is found to be HIV-positive on the 1st of the month. She is given the local standard ART regimen and takes her first dose of ART that same day. Two days later, on the 3rd of the month, she reports to the study clinic, provides informed consent, and undergoes screening evaluations. On the 4th of the month, the mother undergoes fetal ultrasound and is found to be relatively early in her pregnancy: 13 weeks plus 2 days.

SUN	MON	TUE	WED	THU	FRI	SAT
		1 Starts ART	2	3 Starts Screening	4 U/S shows 13w+2d	5
6	7	8	9 First day to enroll	10	11	12
13	14 Last day to enroll	15	16	17	18	19
20	21	22	23	24	25	26

Based on the dates shown above, similar to Example #1, the last possible day for this mother-infant pair to be enrolled is the 14th of the month. In addition, however, the gestational age of the pregnancy must also be taken into consideration. Because enrollment must occur at or after 14 weeks gestation (greater than 13 weeks plus 6 days) the first possible day to enroll this mother-infant pair is the 9th of the month. Therefore, this pair would need to be enrolled between the 9th and 14th of the month (inclusive).

**Example #4:** In this example, the mother presents for antenatal care and is found to be HIV-positive on the 1st of the month. She is given the local standard ART regimen and takes her first dose of ART that same day. Two days later, on the 3rd of the month, she reports to the study clinic, provides informed consent, and undergoes screening evaluations. On the 4th of the month, the mother undergoes fetal ultrasound and is found to be relatively late in her pregnancy: 27 weeks plus 2 days.

SUN	MON	TUE	WED	THU	FRI	SAT
		1 Starts ART	2	3 Starts Screening	4 U/S shows 27w+2d	5
6	7	8 Last day to enroll	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26

Enrollment must occur within 28 completed weeks (27 weeks plus six days) gestation; therefore, the last day to enroll this mother-infant pair is the 8th of the month.

**Figure 4-2a**  
**Sample SES Confirmation File with SIDs for IMPAACT 2010**

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*****
SES (rando 4.0.0.1)
Copyright 2002 FSTRF

PRS Date & Time: [28 February 2018 13:27:56 (GMT-05:00) US Eastern Time]

Enrolling as: [devans.andrew]

Group: [01]  Inst.: [1101]  Study: [2010]  Step: [1]

(M000) *** PATIENT SUCCESSFULLY ENROLLED ***

PRESCRIPTION:
Study entry through pregnancy and delivery and for 50 weeks postpartum.:
- Mothers: Dolutegravir (DTG) , 50 mg tablets , Once daily, orally, with
  or without food
- PLUS Emtricitabine/tenofovir alafenamide (FTC/TAF) , Fixed-dose
  combination tablets (FTC 200 mg/TAF 25 mg) , Once daily, orally, with
  or without food
- Infants: Local standard , prophylaxis per , Protocol Section 8.9

PID: [881001 H]  SID Assignment: [2010 2452 b]

Stratum string: [292]  Balancing: [none]

Child PID: [881002 F]  Child SID Assignment: [2010 2453 l]

*****

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**Figure 4-2b**  
**Sample SES Confirmation File with SIDs for IMPAACT 2010**

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*****
SES (rando 4.0.0.1)
Copyright 2002 FSTRF

PRS Date & Time: [26 March 2018 16:20:54 (GMT-04:00) US Eastern Time]

Enrolling as: [devans.andrew]

Group: [01] Inst.: [1101] Study: [2010] Step: [1]

(M000) *** PATIENT SUCCESSFULLY ENROLLED ***

PRESCRIPTION:
Study entry through pregnancy and delivery and for 50 weeks postpartum.:
- Mothers: Dolutegravir (DTG) , 50 mg tablets , Once daily, orally, with
  or without food
- PLUS Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) , Fixed-dose
  combination tablets (FTC 200 mg/TDF 300 mg) , Once daily, orally, with
  or without food
- Infants: Local standard , prophylaxis per , Protocol Section 8.9

PID: [789005 E] SID Assignment: [2010 2442 c]

Stratum string: [292] Balancing: [none]

Child PID: [789006 B] Child SID Assignment: [2010 2443 a]

*****
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**Figure 4-2c**  
**Sample SES Confirmation File with SIDs for IMPAACT 2010**

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*****
SES (rando 4.0.0.1)
Copyright 2002 FSTRF

PRS Date & Time: [26 March 2018 16:17:00 (GMT-04:00) US Eastern Time]

Enrolling as: [devans.andrew]

Group: [01] Inst.: [1101] Study: [2010] Step: [1]

(M000) *** PATIENT SUCCESSFULLY ENROLLED ***

PRESCRIPTION:
Study entry through pregnancy and delivery and for 50 weeks postpartum.:
- Mothers: Efavirenz/(emtricitabine)/tenofovir disoproxil fumarate
  [EFV/FTC/TDF] , Fixed-dose combination tablets [EFV 600 mg/(FTC 200
  mg)/TDF 300 mg] , Once daily, orally, on an empty stomach, preferably
  at bed time
- Infants: Local standard , prophylaxis per , Protocol Section 8.9

PID: [789003 I] SID Assignment: [2010 2412 f]

Stratum string: [292] Balancing: [none]

Child PID: [789004 G] Child SID Assignment: [2010 2413 d]

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#### 4.3.6 FAQs Related to Enrollment

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

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

**4-X Protocol Section 6.1 allows for repeat screening attempts. Although we think such attempts will be rare, we would like to know how Screening ID numbers should be handled on this setting. Would we need to assign a second Screening ID for the second screening attempt?**

Yes. For the first screening attempt, you would need to enter a Screening Failure and Non-Enrollment Results eCRF (SCR10001) to close out that attempt. Presumably, the reason for non-enrollment recorded on this form will be “Mother-infant pair could not be enrolled within the protocol-specified timeframes due to administrative or logistical issues.” Then, when the second screening attempt is initiated, following completion of a second informed consent process, a second Screening ID should be assigned using the Subject Enrollment System.

**4-Y In the event that a woman who is pregnant with twins is enrolled in the study, how do we go about enrolling the second twin?**

You are correct that the second twin should be enrolled in the study. The enrollment will need to be performed manually at the Data Management Center (DMC). Please contact the DMC’s Randomization Support Office (email [rando.support@fstfrf.org](mailto:rando.support@fstfrf.org) or call +716-834-0900 x7301) and be prepared to provide the PID assigned to the mother and the PID assigned to the second twin.

**4-Z When we try to enter eligibility information into the IMPAACT Screening Checklist (PS2001) in the Subject Enrollment System, we have received an error message as follows: “Inst [####] does not have permission to enroll to study [IMPAACT2010] and/or the study/step is not open to accrual.” However, we are activated to start the study. Can you help?**

The screening attempt failed because you entered “IMPAACT2010” in Q0002 of the IMPAACT Screening Checklist. To successfully obtain a screening number, you need to enter “2010” in this question. Please try again using the correct study number and contact the DMC’s Randomization Support Office (email [rando.support@fstfrf.org](mailto:rando.support@fstfrf.org) or call +716-834-0900 x7301) if you have other challenges.

#### 4.3.7 Screening and Enrollment Logs

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

## Section 4 Appendix

### Determining Eligibility based on Gestational Age

Inclusion criterion 4.1.6 requires that mothers be enrolled at 14-28 weeks gestation, which is defined as greater than 13 weeks plus six days and up to 27 weeks plus six days.

The published American College of Obstetricians and Gynecologists (ACOG) method for determining gestational age, which is presented on the next four pages, should be used when assessing gestational age for purposes of eligibility determination. In addition to referring to the ACOG publication, site clinicians are encouraged to use the ACOG app, which includes calculator tools that are programmed consistent with the published ACOG method; see also: <http://www.acog.org/acogapp>.

The ACOG method requires consideration of gestational age estimated based on the date of last menstrual period and gestational age estimated based on fetal ultrasound findings. Consistent with protocol Section 6.13, ultrasound result reports should include the following:

- Date of scan
- Number of fetuses
- Estimated fetal weight if greater than 20 completed weeks gestation
- Biometry measures
  - If less than 14 weeks gestation:
    - Crown-rump length
  - If 14 or more weeks gestation:
    - Femur length
    - Abdominal circumference
    - Biparietal diameter and/or head circumference
- Ultrasound-based gestational age on the date of the scan or ultrasound-based estimated date of delivery

*Note:* Sites are responsible for entering the above-listed ultrasound findings into eCRFs; these data are needed to ascertain primary study outcomes. Although the protocol allows for either biparietal diameter or head circumference to be entered (if 14 or more weeks gestation), both of these measurements should be entered whenever available. If only one of these two measurements is available, head circumference is preferred for use in standard algorithms to determine gestational age at birth.

An ultrasound-based gestational age on the date of the scan or ultrasound-based estimated date of delivery is needed when using the ACOG method to determine gestational age. In the event that an ultrasound result report does not include an ultrasound-based gestational age or ultrasound-based estimated date of delivery, these can be calculated from the ultrasound-based biometry measures using Intergrowth 21st Consortium tools, which are available at:

<https://intergrowth21.tghn.org/intergrowth-21st-applications/>

Please contact the CMC with any questions related to this section appendix, the ACOG method, or determining eligibility based on gestational age for any potential participant.



The American College of  
Obstetricians and Gynecologists  
WOMEN'S HEALTH CARE PHYSICIANS



# COMMITTEE OPINION

Number 700 • May 2017

(Replaces Committee Opinion Number 611, October 2014)

## Committee on Obstetric Practice American Institute of Ultrasound in Medicine Society for Maternal-Fetal Medicine

*This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice, in collaboration with members Christian M. Pettker, MD; James D. Goldberg, MD; and Yasser Y. El-Sayed, MD; the American Institute of Ultrasound in Medicine's liaison member Joshua A. Copel, MD; and the Society for Maternal-Fetal Medicine.*

*This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.*

## Methods for Estimating the Due Date

**ABSTRACT:** Accurate dating of pregnancy is important to improve outcomes and is a research and public health imperative. As soon as data from the last menstrual period, the first accurate ultrasound examination, or both are obtained, the gestational age and the estimated due date (EDD) should be determined, discussed with the patient, and documented clearly in the medical record. Subsequent changes to the EDD should be reserved for rare circumstances, discussed with the patient, and documented clearly in the medical record. A pregnancy without an ultrasound examination that confirms or revises the EDD before 22 0/7 weeks of gestational age should be considered suboptimally dated. When determined from the methods outlined in this document for estimating the due date, gestational age at delivery represents the best obstetric estimate for the purpose of clinical care and should be recorded on the birth certificate. For the purposes of research and surveillance, the best obstetric estimate, rather than estimates based on the last menstrual period alone, should be used as the measure for gestational age.

### Recommendations

The American College of Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine, and the Society for Maternal-Fetal Medicine make the following recommendations regarding the method for estimating gestational age and due date:

- Ultrasound measurement of the embryo or fetus in the first trimester (up to and including 13 6/7 weeks of gestation) is the most accurate method to establish or confirm gestational age.
- If pregnancy resulted from assisted reproductive technology (ART), the ART-derived gestational age should be used to assign the estimated due date (EDD). For instance, the EDD for a pregnancy that resulted from in vitro fertilization should be assigned using the age of the embryo and the date of transfer.
- As soon as data from the last menstrual period (LMP), the first accurate ultrasound examination, or both are obtained, the gestational age and the EDD should be determined, discussed with the patient, and documented clearly in the medical record. Subsequent changes to the EDD should be reserved for rare circumstances, discussed with the patient, and documented clearly in the medical record.
- When determined from the methods outlined in this document for estimating the due date, gestational age at delivery represents the best obstetric estimate for the purpose of clinical care and should be recorded on the birth certificate. For the purposes of research and surveillance, the best obstetric estimate, rather than estimates based on the LMP alone, should be used as the measure for gestational age.

- A pregnancy without an ultrasound examination that confirms or revises the EDD before 22 0/7 weeks of gestational age should be considered suboptimally dated.

## Introduction

An accurately assigned EDD early in prenatal care is among the most important results of evaluation and history taking. This information is vital for timing of appropriate obstetric care; scheduling and interpretation of certain antepartum tests; determining the appropriateness of fetal growth; and designing interventions to prevent preterm births, postterm births, and related morbidities. Appropriately performed obstetric ultrasonography has been shown to accurately determine fetal gestational age (1). A consistent and exacting approach to accurate dating is also a research and public health imperative because of the influence of dating on investigational protocols and vital statistics. This Committee Opinion outlines a standardized approach to estimate gestational age and the anticipated due date. It is understood that within the ranges suggested by different studies, no perfect evidence exists to establish a single-point cutoff in the difference between clinical and ultrasonographic EDD to prompt changing a pregnancy's due date. However, there is great usefulness in having a single, uniform standard within and between institutions that have access to high-quality ultrasonography (as most, if not all, U.S. obstetric facilities do). Accordingly, in creating recommendations and the associated summary table, single-point cutoffs were chosen based on expert review.

## Background

Traditionally, determining the first day of the LMP is the first step in establishing the EDD. By convention, the EDD is 280 days after the first day of the LMP. Because this practice assumes a regular menstrual cycle of 28 days, with ovulation occurring on the 14th day after the beginning of the menstrual cycle, this practice does not account for inaccurate recall of the LMP, irregularities in cycle length, or variability in the timing of ovulation. It has been reported that approximately one half of women accurately recall their LMP (2–4). In one study, 40% of the women randomized to receive first-trimester ultrasonography had their EDD adjusted because of a discrepancy of more than 5 days between ultrasound dating and LMP dating (5). Estimated due dates were adjusted in only 10% of the women in the control group who had ultrasonography in the second trimester, which suggests that first-trimester ultrasound examination can improve the accuracy of the EDD, even when the first day of the LMP is known.

Accurate determination of gestational age can positively affect pregnancy outcomes. For instance, one study found a reduction in the need for postterm induc-

tions in a group of women randomized to receive routine first-trimester ultrasonography compared with women who received only second-trimester ultrasonography (5). A Cochrane review concluded that ultrasonography can reduce the need for postterm induction and lead to earlier detection of multiple gestations (6). Because decisions to change the EDD significantly affect pregnancy management, their implications should be discussed with patients and recorded in the medical record.

## Clinical Considerations in the First Trimester

Ultrasound measurement of the embryo or fetus in the first trimester (up to and including 13 6/7 weeks of gestation) is the most accurate method to establish or confirm gestational age (3, 4, 7–10). Up to and including 13 6/7 weeks of gestation, gestational age assessment based on measurement of the crown–rump length (CRL) has an accuracy of  $\pm 5$ –7 days (11–14). Measurements of the CRL are more accurate the earlier in the first trimester that ultrasonography is performed (11, 15–18). The measurement used for dating should be the mean of three discrete CRL measurements when possible and should be obtained in a true midsagittal plane, with the genital tubercle and fetal spine longitudinally in view and the maximum length from cranium to caudal rump measured as a straight line (8, 11). Mean sac diameter measurements are not recommended for estimating the due date. Beyond measurements of 84 mm (corresponding to approximately 14 0/7 weeks of gestation), the accuracy of the CRL to estimate gestational age decreases, and in these cases, other second-trimester biometric parameters (discussed in the following section) should be used for dating. If ultrasound dating before 14 0/7 weeks of gestation differs by more than 7 days from LMP dating, the EDD should be changed to correspond with the ultrasound dating. Dating changes for smaller discrepancies are appropriate based on how early in the first trimester the ultrasound examination was performed and clinical assessment of the reliability of the LMP date (Table 1). For instance, before 9 0/7 weeks of gestation, a discrepancy of more than 5 days is an appropriate reason for changing the EDD. If the patient is unsure of her LMP, dating should be based on ultrasound examination estimates (ideally obtained before or at 13 6/7 weeks of gestation), with the earliest ultrasound examination of a CRL measurement prioritized as the most reliable.

If pregnancy resulted from ART, the ART-derived gestational age should be used to assign the EDD. For instance, the EDD for a pregnancy that resulted from in vitro fertilization should be assigned using the age of the embryo and the date of transfer. For example, for a day-5 embryo, the EDD would be 261 days from the embryo replacement date. Likewise, the EDD for a day-3 embryo would be 263 days from the embryo replacement date.



## Clinical Considerations in the Second Trimester

Using a single ultrasound examination in the second trimester to assist in determining the gestational age enables simultaneous fetal anatomic evaluation. However, the range of second-trimester gestational ages (14 0/7 weeks to 27 6/7 weeks of gestation) introduces greater variability and complexity, which can affect revision of LMP dating and assignment of a final EDD. With rare exception, if a first-trimester ultrasound examination was performed, especially one consistent with LMP dating, gestational age should not be adjusted based on a second-trimester ultrasound examination. Ultrasonography dating in the second trimester typically is based on regression formulas that incorporate variables such as

- the biparietal diameter and head circumference (measured in transverse section of the head at the level of the thalami and cavum septi pellucidi; the cerebellar hemispheres should not be visible in this scanning plane)
- the femur length (measured with full length of the bone perpendicular to the ultrasound beam, excluding the distal femoral epiphysis)
- the abdominal circumference (measured in symmetrical, transverse round section at the skin line, with visualization of the vertebrae and in a plane with visualization of the stomach, umbilical vein, and portal sinus) (8)

Other biometric variables, such as additional long bones and the transverse cerebellar diameter, also can play a role.

Gestational age assessment by ultrasonography in the first part of the second trimester (between 14 0/7 weeks and 21 6/7 weeks of gestation, inclusive) is based on a composite of fetal biometric measurements and has an accuracy of  $\pm 7$ –10 days (19–22). If dating by ultrasonography performed between 14 0/7 weeks and 15 6/7 weeks of gestation (inclusive) varies from LMP dating by more than 7 days, or if ultrasonography dating between 16 0/7 weeks and 21 6/7 weeks of gestation varies by more than 10 days, the EDD should be changed to correspond with the ultrasonography dating (Table 1). Between 22 0/7 weeks and 27 6/7 weeks of gestation, ultrasonography dating has an accuracy of  $\pm 10$ –14 days (19). If ultrasonography dating between 22 0/7 weeks and 27 6/7 weeks of gestation (inclusive) varies by more than 14 days from LMP dating, the EDD should be changed to correspond with the ultrasonography dating (Table 1). Date changes for smaller discrepancies (10–14 days) are appropriate based on how early in this second-trimester range the ultrasound examination was performed and on clinician assessment of LMP reliability. Of note, pregnancies without an ultrasound examination that confirms or revises the EDD before 22 0/7 weeks of gestational age should be considered suboptimally dated (see also Committee Opinion 688, *Management of Suboptimally Dated Pregnancies* [23]).

## Clinical Considerations in the Third Trimester

Gestational age assessment by ultrasonography in the third trimester (28 0/7 weeks of gestation and beyond) is the least reliable method, with an accuracy of  $\pm 21$ –30 days (19, 20, 24). Because of the risk of redating

**Table 1.** Guidelines for Redating Based on Ultrasonography ↵

Gestational Age Range*	Method of Measurement	Discrepancy Between Ultrasonography Dating and LMP Dating That Supports Redating
≤13 6/7 wk	CRL	
• ≤ 8 6/7 wk		More than 5 d
• 9 0/7 wk to 13 6/7 wk		More than 7 d
14 0/7 wk to 15 6/7 wk	BPD, HC, AC, FL	More than 7 d
16 0/7 wk to 21 6/7 wk	BPD, HC, AC, FL	More than 10 d
22 0/7 wk to 27 6/7 wk	BPD, HC, AC, FL	More than 14 d
28 0/7 wk and beyond†	BPD, HC, AC, FL	More than 21 d

Abbreviations: AC, abdominal circumference; BPD, biparietal diameter; CRL, crown–rump length; FL, femur length; HC, head circumference; LMP, last menstrual period.

\*Based on LMP.

†Because of the risk of redating a small fetus that may be growth restricted, management decisions based on third-trimester ultrasonography alone are especially problematic and need to be guided by careful consideration of the entire clinical picture and close surveillance.

a small fetus that may be growth restricted, management decisions based on third-trimester ultrasonography alone are especially problematic; therefore, decisions need to be guided by careful consideration of the entire clinical picture and may require close surveillance, including repeat ultrasonography, to ensure appropriate interval growth. The best available data support adjusting the EDD of a pregnancy if the first ultrasonography in the pregnancy is performed in the third trimester and suggests a discrepancy in gestational dating of more than 21 days.

## Conclusion

Accurate dating of pregnancy is important to improve outcomes and is a research and public health imperative. As soon as data from the LMP, the first accurate ultrasound examination, or both are obtained, the gestational age and the EDD should be determined, discussed with the patient, and documented clearly in the medical record. Subsequent changes to the EDD should be reserved for rare circumstances, discussed with the patient, and documented clearly in the medical record. When determined from the methods outlined in this document for estimating the due date, gestational age at delivery represents the best obstetric estimate for the purpose of clinical care and should be recorded on the birth certificate. For the purposes of research and surveillance, the best obstetric estimate, rather than estimates based on the LMP alone, should be used as the measure for gestational age. A pregnancy without an ultrasound examination that confirms or revises the EDD before 22 0/7 weeks of gestational age should be considered suboptimally dated.

The American College of Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine, and the Society for Maternal–Fetal Medicine recognize the advantages of a single dating paradigm being used within and between institutions that provide obstetric care. Table 1 provides guidelines for estimating the due date based on ultrasonography and the LMP in pregnancy, and provides single-point cutoffs and ranges based on available evidence and expert opinion.

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## **Section Appendix 4-2**

### **Maternal HIV Testing Requirements**

Under protocol Version 2.0, inclusion criterion 4.1.2 requires confirmation of maternal HIV-1 infection prior to study entry and exclusion criterion 4.2.4 requires exclusion of mothers with a history of HIV-2 infection.

Although there is no epidemiologic evidence of HIV-2 circulating in countries where IMPAACT 2010 sites are located, for regulatory compliance with the wording of the study eligibility criteria, the Protocol Team has determined that all sites must include at least one test in their maternal HIV testing algorithm that can distinguish HIV-1 from HIV-2.

Tests that meet the requirements specified for Sample #1 and Sample #2 in inclusion criterion 4.1.2, and that can distinguish HIV-1 from HIV-2, include but are not limited to the Geenius™ HIV 1/2 Supplemental Assay, Bio-Rad Western blot, and HIV-1 RNA PCR assays. With more specific reference to the Sample #1 and Sample #2 requirements, it is acceptable to use HIV 1/2 antibody tests for Sample #1, provided that a test that can distinguish HIV-1 and HIV-2 is used for Sample #2.

As a reminder, the Sample #1 and Sample #2 tests performed to confirm maternal HIV infection are not entered into laboratory eCRFs for this study. Instead, confirmation of this inclusion criterion is entered into the Subject Enrollment System. Adequate source documentation of each test performed must be available in each participant's study chart to substantiate entries made into the Subject Enrollment System.

For all enrolled mothers, HIV infection should be entered into the Medical History Log eCRF (MHW10001).

## 5.0 INFORMED CONSENT

This section contains reference information and guidance for obtaining informed consent in IMPAACT 2010. This study involves three different informed consent processes:

- ***Informed consent for mother and infant study participation:*** Informed consent for mother and infant study participation must be obtained before any study-specific screening or on-study procedures are performed. Each mother will provide written informed consent for her own participation in the study and, unless otherwise specified by site IRBs/ECs, will provide written informed consent for her infant's participation in the study.

As noted in protocol Section 12.3, and as reflected in the sample informed consent forms in protocol Appendices III and IV, it is generally expected that mothers will provide informed consent for their own and their infant's participation in the study. However, parental consenting requirements at each site will depend on the IRB/EC risk determination for the study. If the IRB/EC risk determination requires the consent of both parents, in addition to the mother providing informed consent for infant participation, the father should also provide informed consent if he is reasonably available at the study clinic. In this scenario, the site would need to adapt the signature pages of their informed consent forms to accommodate both maternal and paternal consent and, if the father is reasonably available at the study clinic, he should document his consent in the signature block for fathers. If the father is reasonably available at the study clinic, and declines consent, the mother-infant pair should not be enrolled in the study. If the father is not reasonably available at the study clinic, this should be documented in source documents and the father's signature block should be left blank. In this case, the mother-infant pair may be enrolled based on the mother's consent.

- ***Informed consent for maternal and infant specimen storage and future use:*** Informed consent must be requested for storage and future research of maternal and infant specimens that are left over after all protocol-specified testing has been performed. This informed consent process need not be conducted prior to study entry but should ideally be conducted as soon as possible and within three months after study entry. Mothers may choose to either provide or decline informed consent for specimen storage and future use — for themselves and/or for their infants — with no impact on other aspects of their study participation. As indicated on the sample signature page in protocol Appendix IV, this informed consent form must be signed or marked regardless of whether informed consent is provided or declined. In addition, specific notations must be recorded on the form to document consent decisions — for mother and infant — for genetic testing.
- ***Informed consent for use of study drug during subsequent pregnancy:*** For any mother who experiences a new pregnancy while in study follow-up, informed consent must be obtained for continued use of study drug during the new pregnancy. This informed consent process should take place as soon as possible after identifying a new pregnancy, before any further study drugs are dispensed to the mother. As indicated on the sample signature page in protocol Appendix V, this informed consent form must be signed or marked by the mother regardless of whether she chooses to receive one or more study drugs during the new pregnancy.

The remainder of this section provides background information and operational guidance that is applicable to all the informed consent processes noted above. Figure 5-1 provides further guidance for obtaining re-consent for protocol Version 2.0 for participants enrolled under protocol Version 1.0. Figure 5-2 provides further guidance for obtaining re-consent for continued study participation under LoA #1.

**Figure 5-1**  
**Re-Consenting Considerations for Protocol Version 2.0**

*Refer as needed to the Summary of Changes document for Protocol Version 2.0*

Following the issuance of protocol Version 2.0 in December 2017, sites were required to prepare site-specific informed consent forms (ICFs) for protocol Version 2.0 and submit these for IRB/EC review and approval; approval is also required from other site regulatory entities if applicable per the policies and procedures of these entities.

At each site, once all required approvals are obtained, the Version 2.0 ICFs should immediately be used for all newly consented participants. In addition, unless otherwise directed by site IRBs/ECs, previously-enrolled participants must be re-consented for maternal and infant study participation using the Version 2.0 ICFs, as follows:

- At the next study visit after all required approvals are obtained, re-consent for ongoing participation should be obtained using the Version 2.0 ICF, before any study-specific procedures are performed.
  - The same parental consenting requirements (referenced on page 33) that were applicable for study participation under protocol Version 1.0 also apply for re-consenting under protocol Version 2.0.
  - The re-consenting process should be documented in participant study charts and relevant data should be entered into the LGW10000 eCRF.
  - In the event that informed consent for ongoing participation in IMPAACT 2010 protocol Version 2.0 is declined (expected to be rare), the participant(s) must be withdrawn from the study. If possible, an Early Discontinuation visit should be conducted per the Schedule of Evaluations and protocol Section 6.9 of protocol Version 1.0.
- Unless otherwise directed by site IRBs/ECs, re-consenting is not required for specimen storage and future use.

**Figure 5-2**  
**Re-Consenting Considerations for Protocol Version 2.0 LoA #1**

*Refer as needed to the Information/Instructions to Study Sites from the Division of AIDS  
on page 2 of LoA #1*

Following the issuance of protocol Version 2.0 LoA #1 in July 2018, sites are required to prepare site-specific informed consent forms (ICFs) corresponding to LoA #1 and submit these for IRB/EC review and approval; approval is also required from other site regulatory entities if applicable per the policies and procedures of these entities.

At each site, following issuance of the Implementation Notice for LoA #1, and once all required approvals are obtained, revised ICFs corresponding to LoA #1 should immediately be used for all newly consented participants. In addition, unless otherwise directed by site IRBs/ECs, previously-enrolled participants must be re-consented for maternal and infant study participation using the revised ICFs, as follows:

- At the next study visit after issuance of the Implementation Notice and all required approvals have been obtained, re-consent for ongoing participation should be obtained using the revised ICF before any study-specific procedures are performed.
  - The same parental consenting requirements (referenced on page 33) that were applicable for study participation under protocol Version 1.0 and Version 2.0 also apply for re-consenting under LoA #1.
  - The re-consenting process should be documented in participant study charts and relevant data should be entered into the LGW10000 eCRF:

*At the visit when the ICF corresponding to LoA #1 is signed or marked:*

- Complete the IMPAACT 2010 Study Event Tracking – Maternal eCRF (SVW10001) and select YES for item 2, At this visit or since the last visit, has the mother’s informed consent status changed? Answer other items as applicable for each mother.
- Selecting YES for item 2 on the SVW10001 will prompt an update of the Informed Consent Status Log eCRF (LGW10000).
- Enter a new log line into the Informed Consent Status Log eCRF (LGW10000) as follows:
  - Select “Protocol Version 2.0 LoA 1” for item 1, Indicate the type of consent or deconsent.
  - Select PROVIDED for item 2, Status.
  - Enter the date the mother signed or marked the revised ICF under LoA #1 as the DATE OF CONSENT.
- Enter all other applicable eCRFs for the mother and infant (if born).
- In the event that informed consent for ongoing participation in IMPAACT 2010 protocol Version 2.0 is declined (expected to be rare), the participant(s) must be withdrawn from the study. If possible, an Early Discontinuation visit should be conducted per the Schedule of Evaluations and protocol Section 6.9 of protocol Version 2.0.

Unless otherwise directed by site IRBs/ECs, re-consenting is not required for specimen storage and future use.

## 5.1 General Considerations for Obtaining Informed Consent

Informed consent is a process by which an individual voluntarily expresses his or her willingness to participate in research, after having been informed of all aspects of the research that are relevant to the decision. Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process involving information exchange, comprehension, voluntariness, and documentation. Each of these aspects of the informed consent process is described in greater detail below. Please also refer to Section 4.8 of the International Conference on Harmonization (ICH) *Consolidated Guidance for Good Clinical Practice* (GCP) and the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* for further information.

US regulations (45 CFR 46 and 21 CFR 56) specify the elements of informed consent that must be conveyed to consenters through the informed consent process. It is the responsibility of the IoR, and by delegation all study staff involved in conducting the informed consent process, to deliver all required information to consenters.

Based on the reviews completed as part of the IMPAACT 2010 protocol development and study activation processes, there is adequate assurance that once a site-specific study activation notice has been issued, a site's informed consent forms (ICFs) include all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate ICF. It also is the responsibility of the IoR and designated study staff to:

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

Further guidance related to each of these requirements is provided in Sections 5.2-5.5 below. Each site must have on file a study-specific SOP for obtaining informed consent that addresses all aspects of the informed consent process consistent with all applicable regulations, DAIDS policies and procedures, and protocol specifications. All sites must follow their SOPs consistently for all IMPAACT 2010 informed consent processes. All site staff involved in obtaining informed consent must be designated on the study-specific delegation of duties log and listed on the Form FDA 1572 for the study. These staff must be qualified by education, experience, training, and knowledge of the study, as determined by the IoR, and appropriate training documentation must be available to support the IoR's delegation to these staff.

### IMPORTANT NOTE

Per protocol Section 12.3, should the consenting mother of an enrolled infant die or no longer be available for any reason, all applicable IRB/EC policies and procedures should be followed; however, no further study-specific infant evaluations should be performed until informed consent for continued study participation is obtained from the infant's 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 local standards of care, but no study-specific procedures (outside of the standard of care) may be performed. If an authorized guardian cannot be identified, or if the authorized guardian does not consent to continued study participation, the infant must be withdrawn from the study. In accordance with the DAIDS policy on *Enrolling Children (including Adolescents) in Clinical Research*, all sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled infant, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

## **5.2 Deliver all Required Information in a Manner that is Understandable to the Consenter**

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

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

If the consenter is not literate, an impartial literate witness must be present during the entire informed consent process. As part of the documentation steps detailed below, the witness will be asked to sign and date the ICF to attest that the information in the ICF was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter. ICH-E6 identifies an "impartial" witness as a person who is independent of the study, who cannot be unfairly influenced by people involved with the study. The IMPAACT Operations Center has previously received guidance from the US Food and Drug Administration's GCP office stating that the witness need not be "totally unaffiliated with the study. It may be possible, for example, to designate a "subject advocate" who would be available at each site ..." Sites with questions about who may serve as an impartial witness are encouraged to consult with their IRBs/ECs on possible options. Refer to Figure 5-3 for a summary of considerations for obtaining informed consent from illiterate consenters. Figure 5-4 provides an example of completion of informed consent signature blocks for illiterate consenters.

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

During informed consent discussions, take care to not overstate the possible benefits of the study, nor to understate the risks. Also describe the alternatives to study participation and emphasize that the availability of medical care and other services (outside the study) will not be affected by the consenter's decision whether to take part in the study. Encourage the consenter to take as much time as she needs — and to talk about study participation with others if she chooses — before making a decision.

When a witness is present during the informed consent process, care should be taken to minimize the perception of coercion due to the presence of the witness. For example, the purpose of having the witness present should be clearly explained to the consenter, with emphasis on the fact that the witness is there as a protection for the consenter, not as an agent of the study per se.

## **5.4 Confirm that the Consenter Comprehends the Information**

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

A variety of approaches can be taken to assess comprehension. One approach uses a semi-structured checklist to guide a discussion in which the consenter responds to open-ended questions designed to elicit her understanding of key concepts. A sample checklist of this type, with accompanying instructions for use, is provided in Figure 5-5. Other approaches may include documented discussions with the consenter as well as structured knowledge quizzes administered to the consenter.

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

## **5.5 Document the Process**

US regulations require that informed consent be documented through the use of a written informed consent form approved by the IRB/EC and signed and dated by the consentor or the consentor's legally authorized representative at the time of consent.

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

If the consentor is not literate, the witness who was present during the informed consent process must sign and date the ICF to attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the consentor, and that informed consent was freely given by the consentor. The consentor's printed name, signature, and signature date blocks on the ICF should be completed as described in Figure 5-3.

The DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* lists detailed requirements and suggestions for documenting the informed consent process. Study sites must comply with all requirements and are encouraged to comply with all suggestions. To assist with compliance, study staff may use informed consent coversheets similar to the example provided in Figure 5-6. Sites choosing to use coversheets should identify the coversheets as source documents in their study-specific SOPs for source documentation and should use the coversheets consistently to document each informed consent process conducted with each consentor. All informed consent documentation must be maintained on file in participant study records.

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



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

- Informed consent for mother and infant study participation will be entered into the LGW10000, IMPAACT 2010 Informed Consent Status Log eCRF.
  - For Mothers: At Entry and anytime the informed consent status changes for the mother:
    - Complete the IMPAACT 2010 Study Event Tracking – Maternal eCRF (SVW10001) and select YES for item 2, At this visit or since the last visit, has the mother’s informed consent status changed? Answer other items as applicable for each mother.
    - Selecting YES for item 2 of the SVW10001 will prompt an update of the Informed Consent Status Log eCRF (LGW10000), in the Participant Logs folder.
    - Enter a new log line into the Informed Consent Status Log eCRF (LGW10000). Indicate the mother’s initial informed consent status and any changes of the mother’s informed consent status after study entry. This includes all protocol versions and LoAs, as well as any other informed consent decisions.  
*Note:* Consent for specimen storage and future use is recorded on the TRK10000 eCRF and not on the LGW10000 eCRF.
  - For Infants: At Delivery and anytime the informed consent status changes for the infant:
    - Complete the IMPAACT 2010 Study Event Tracking – Infant eCRF (SVW10000) and select YES for item 2, At this visit or since the last visit, has the infant's informed consent status changed? Answer other items as applicable for the infant.
    - Selecting YES for item 2 of the SVW10000 will prompt an update of the Informed Consent Status Log eCRF (LGW10000), in the Participant Logs folder.
    - Enter a new log line into the Informed Consent Status Log eCRF (LGW10000). Indicate the infant’s initial informed consent status and any changes to the infant’s informed consent status after delivery. This includes all protocol versions and LoAs, as well as any other informed consent decisions.  
*Note:* Consent for specimen storage and future use is recorded on the TRK10000 eCRF and not on the LGW10000 eCRF.
- Informed consent for use of study drug during a subsequent pregnancy will be entered into the LGW10000, IMPAACT 2010 Informed Consent Status Log eCRF.
  - For mothers who experience a subsequent pregnancy while on-study:
    - Complete the IMPAACT 2010 Study Event Tracking – Maternal eCRF (SVW10001) and select YES for item 2, At this visit or since the last visit, has the mother’s informed consent status changed? Answer other items as applicable for each mother.
    - Selecting YES for item 2 of the SVW10001 will prompt an update of the Informed Consent Status Log eCRF (LGW10000), in the Participant Logs folder.
    - Enter a new log line into the Informed Consent Status Log eCRF (LGW10000) as follows: Select “Study drug use during subsequent pregnancy” for item 1, Indicate the type of consent or deconsent.
      - If the mother consented to take ARVs from the study during the subsequent pregnancy, select PROVIDED for item 2, Status, and enter the date the mother signed or marked the ICF as the DATE OF CONSENT.
      - If the mother did not consent to take ARVs from the study during the subsequent pregnancy, select NOT PROVIDED for item 2, Status, and enter the date the mother signed or marked the ICF as the DATE OF DECONSENT.

- Informed consent for maternal and infant specimen storage and future use will be entered into the TRK10000, Specimen Consent for Non-Protocol Defined Testing eCRF. Per protocol Section 12.3, mothers will be asked to provide written informed consent for storage and future research testing (including genetic testing) of biological specimens remaining after protocol-specified testing has been completed. This consent process may be conducted at any time during study participation but ideally as soon as possible and within three months after study entry.
- For Mothers: The Specimen Consent for Non-Protocol Defined Testing eCRF (TRK10000) is indicated for completion in the Screening visit folder. If this consent changes for the mother after study entry, another TRK10000 eCRF will need to be completed, as follows:
  - Complete the IMPAACT 2010 Study Event Tracking – Maternal eCRF (SVW10001) and select YES for item 3, At this visit or since the last visit, has the mother’s specimen consent status changed? Answer other items as applicable for each mother.
  - Selecting YES for item 3 of the SVW10001 will make another Specimen Consent for Non-Protocol Defined Testing eCRF (TRK10000) available within the study visit folder for completion.
- For Infants: The Specimen Consent for Non-Protocol Defined Testing eCRF (TRK10000) is indicated for completion in the Infant Delivery visit folder. If this consent changes for the infant after delivery, another TRK10000 eCRF will need to be completed at the study visit when this consent changes, as follows:
  - Complete the IMPAACT 2010 Study Event Tracking – Infant eCRF (SVW10000) and select YES for item 3, At this visit or since the last visit, has the infant’s specimen consent status changed? Answer other items as applicable for each infant.
  - Selecting YES for item 3 of the SVW10000 will make another Specimen Consent for Non-Protocol Defined Testing eCRF (TRK10000) available within the study visit folder for completion.

Regulations require that consenters be given a signed copy of their ICF. If a consentor opts not to receive a copy, this should be documented, and the consentor should be offered an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full ICF.

## 5.6 FAQs

- 5-A What should we do if, during the informed consent process, a mother indicates that she would like to take part in the study but is not willing to undergo certain procedures, such as hair collection, DXA scan, or photographing of her infant? We are aware that some site IRBs/ECs require separate informed consent signatures for these procedures, whereas others (including at our site) do not.**

The protocol team would generally advise against enrolling these mothers — in relation to the inclusion criterion requiring willingness and ability to provide informed consent for study participation — especially given that the protocol and sample informed consent form does not include an “opt out” provision for any procedures.

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

- 5-B What should we do if, during re-consenting for LoA #1, a mother indicates that she would like to become pregnant again soon, before she reaches Week 50 postpartum. Should we stop the re-consenting process and discontinue the mother from the study?**

No. Any such mother should ideally stay on-study as originally planned (through Week 50 postpartum) regardless of her fertility intentions and contraceptive choices. The mother should be informed of her options and, if she is willing to remain on-study, should complete the re-consenting process for LoA #1. If the mother is taking DTG postpartum, and chooses not to use contraception postpartum, she should be switched off DTG, in consultation with the CMC, consistent with the specifications of LoA #1.

- 5-C We would like to clarify some issues related to consent for specimen storage and future use (protocol Appendix IV). For mothers who do not consent to this, which specimens should we collect and which should we not collect?**




The informed consent form for study participation obtains consent for collection of all maternal and infant specimens indicated in the Schedule of Evaluations (SoE) and testing of these specimens as specified in the protocol. Some of the protocol-specified testing is performed in real time and some is planned to be performed after follow-up of all participants is completed. Regardless of when the testing is performed, however, all protocol-specified specimen collection, testing, and storage is covered in the informed consent form for study participation. Therefore, all specimen collection, testing, and storage specified in the protocol be performed for all enrolled mothers and infants (i.e., there are no specimens indicated in the SoE that should not be collected).

The informed consent form for specimen storage and future use obtains consent for storage and future use of specimens that are left over after all protocol-specified testing has been completed. For participants who decline this consent, leftover specimens will be destroyed after all protocol-specified testing has been completed; the Protocol Team will provide explicit instructions related to this when the time comes. To reiterate, however, all specimens indicated in the SoE should be collected from these participants, consistent with the main study informed consent form.

**Figure 5-3**  
**Summary of Considerations for Obtaining Informed Consent from Illiterate Consenters**

- Each site must specify procedures for obtaining and documenting informed consent from illiterate persons in its SOP for obtaining informed consent. These procedures must be consistent with the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* and must be followed each time informed consent is obtained from an illiterate consentor. It is recommended that each site seek IRB/EC review and approval of these procedures.
- An impartial witness must be present during the entire informed consent process with an illiterate consentor. The witness must sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the consentor, and that informed consent was freely given by the consentor.
- The site SOP for obtaining informed consent should define who may serve as the witness to the informed consent process.
- Take care to minimize the perception of coercion due to the presence of the witness.
- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process with the consentor should print the consentor's name below the consentor's printed name line on the informed consent form, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry (see Figure 5-4 below).
- The consentor should make her mark on the consentor's signature line.
- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process with the consentor should enter the date upon which the consentor made her mark on the informed consent form below the consentor's signature date line, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry (see Figure 5-4 below).
- For more information, see Section 4.8 of the ICH GCP guidance and the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*.

**Figure 5-4**  
**Example of Completed Informed Consent Signature Blocks for Illiterate Consenters**

<b>SIGNATURES</b>		
		
Participant Name	Participant Signature	Date
<b>Mary Phiri</b>		<b>25 NOV 2014</b>
<i>Participant name and date written by Martha Moore. MM 25 NOV 2014</i>		
<b>Martha Moore</b>		<b>25 NOV 2014</b>
Name of Staff Person Conducting Consent Discussion	Study Staff Signature	Date
<b>Debra Ross</b>		<b>25 NOV 2014</b>
Witness Name	Witness Signature	Date

**Figure 5-5**  
**Sample Informed Consent Comprehension Checklist for IMPAACT 2010**

**Mother's Identifier**

✓	<b>1. Please tell me what you understand about this study and why it is being done.</b>
	Testing ARVs for pregnant women and their babies.
	Some ARVs being tested are have been used widely throughout the world; others are newer and have not been used as widely. There is little information as of now on use of the new ARVs in pregnant women.
✓	<b>2. Please tell me about the groups of mothers and babies in this study.</b>
	There are three groups.
	Mothers in each group are given different ARVs to take while in the study.
	Depending on their group, some mothers get the newer ARVs; others do not.
	Mothers are placed in their groups by chance — neither mothers nor study staff can choose which group each mother is placed in.
✓	<b>3. What are mothers and babies asked to do if they join this study</b>
	Mothers come for clinic visits about once per month while pregnant.
	While pregnant, mothers have an ultrasound scan to show how long they have been pregnant.
	Mothers and babies come for clinic visits soon after the baby is born and 5 more times in the year after the baby is born.
	Mothers must be willing to use family planning in the year after the baby is born.
	Mothers answer questions about themselves and their babies, have physical exams, and have blood, urine, breast milk, and hair collected for tests.
	Babies have physical exams and have blood and hair collected for tests – including HIV tests.
	At DXA sites: Mothers and babies have scans of their bones.
	Mothers may have extra visits if they get sick or if they change ARVs or if their HIV is not controlled.
	Babies may have extra visits if they get sick or if they test positive for HIV.
✓	<b>4. What are the possible risks for mothers and babies in this study?</b>
	Procedures may cause discomfort ( <i>must mention at least one; see sample ICF #19</i> ).
	ARVs may cause side effects ( <i>must mention at least one; see sample ICF #20-23</i> ).
	Others may treat mothers/babies unfairly for being HIV-positive or for being in the study.
✓	<b>5. What are the possible benefits for mothers and babies in this study?</b>
	There may be no benefit ( <i>may mention one or more possible benefits; see sample ICF #25</i> ).
✓	<b>6. What happens if mothers choose not to join the study?</b>
	Mothers are free to make their own choice about joining or not joining.
	<b>No matter what mothers decide about joining, there will be no effect on access to maternal and child health care outside the study</b>
	No matter what mothers decide about joining, it is important for mothers to take ARVs. Taking ARVs is the best known way for mothers to stay healthy and avoid passing HIV to their babies.
✓	<b>7. How will information about mothers and babies be protected?</b>
	Every effort will be made to keep information private and confidential ( <i>must mention at least one method used by the site, see sample ICF #24</i> ).
✓	<b>8. What should mothers do if they have questions or concerns about their health, the health of their babies, or what is happening in the study?</b>
	<i>Must state how to contact study staff (see sample ICF #29)</i>

**Outcome (mark one)**

- ☐ Mother demonstrated comprehension of all required points  
☐ Mother did not demonstrate comprehension of all required points

**Study Staff Signature and Date**

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

1. The sample informed consent comprehension checklist may be adapted for use at each site.
2. The checklist should be administered after the consenter has completed the informed consent discussion, i.e., after she has read the informed consent form (ICF) or had it read to her and discussed any issues, questions, or concerns she may have. It is generally expected that the checklist will be administered by the same study staff member who conducted the informed consent discussion with the consenter. However, this is not required.
3. The checklist should not be presented to the consenter as a “test,” but rather as a way of double-checking that study staff have fulfilled their responsibility to provide all information needed to make an informed decision about taking part in the study. Study staff members who administer the checklist must be sufficiently knowledgeable about the study to make good judgments about consenters’ comprehension of the informed consent information. They should be thoroughly familiar with the site-specific ICFs as well as with the content of the comprehension checklists. Role-playing is strongly recommended as part of preparation and training on use of the checklists.
4. Each checklist is structured around open-ended questions that correspond to the required elements of informed consent for research. For each question, at least one “required point of comprehension” is listed on the checklist; for some questions, several required points of comprehension are listed. Each open-ended question should be read to the consenter. Then, through discussion and dialogue, the intent is for the consenter to demonstrate comprehension of all required points of comprehension listed for each question. The consenter should not be expected to state each required point of comprehension using the exact same wording that appears on the checklist. Rather, the consenter should demonstrate *in her own words* that she understands each required point.
5. Because the open-ended questions are to be read to consenters, these questions should be translated into local languages. Sites may also translate the required points of comprehension, but this is not as critical as translating the questions, because the required points of comprehension are not read to consenters.
6. For each question, the consenter should ideally demonstrate comprehension of all required points before the study staff member administering the checklist proceeds to the next question. When the consenter demonstrates comprehension of one of the required points, study staff should tick that point in the designated space. If the consenter does not spontaneously address one or more of the required points in her response, study staff should ask another open-ended question to elicit a response about that point. For example, one of the required points in Question 3 of the sample checklist is “Babies may have extra visits if they get sick or if they test positive for HIV.” If the consenter does not mention this in her initial response to Question 3, study staff may say, “You mentioned the visits that will be scheduled for mothers and babies after the baby is born. Can you tell me what you understand about other visits that may be needed for babies?”
7. The sample comprehension checklist has been designed to include points of comprehension that address all information required to make an informed decision about study participation. As such, comprehension of all points should be demonstrated before proceeding to the final informed consent decision and signing or marking of the ICF. Sites may choose to modify the wording of the required points of comprehension to correspond with wording used in their site-specific ICFs. Sites may also add points of comprehension to the checklists. Deletions are not recommended.

8. When responding to the open-ended questions, consenters may report back more information than is included on the checklist. This is acceptable, as long as the required information is reported back. However, if any misinformation is reported back, study staff should explain the correct information before proceeding to another question.
9. Once administration of the comprehension checklist begins, it is possible that the conserter may spontaneously state many of the required points, without each open-ended question being asked. In such cases, study staff should tick the relevant points on the checklist and then ask the remaining questions or probe about the remaining points that the conserter has not yet mentioned. It is acceptable to ask a question that a conserter may have already answered in her response to a previous question. However, if study staff are confident that a previous response was adequate, the specific question or point does not need to be repeated.
10. It is possible that a conserter might state correct information, yet study staff may not be convinced that she truly understands a required point of comprehension. In such cases, the study staff member should decide if further explanation or discussion is needed before proceeding to the final informed consent decision and signing or marking of the ICF. Further explanation or discussion may take place at the same visit or at another visit. The assessment process may also take place over the course of multiple days if the conserter becomes fatigued and/or if more time is needed for any other reason.
11. Whenever additional information or explanation is needed to help ensure the conserter's comprehension, any informed consent support materials may be used (e.g., the ICF, other visual aids) to help provide the necessary information. After additional information or explanation is provided, open-ended questions should again be asked to confirm the conserter's comprehension of the required points. Some consenters may be more comfortable interacting with the same study staff member throughout the informed consent process and comprehension assessment. However, another staff member may be consulted, if necessary or desired, to help explain difficult concepts and/or respond to specific questions or concerns.
12. The sample comprehension checklist has been designed as a source document, which should be completed, handled, and retained in participant study records like any other source documents. Relevant conserter and participant identifiers should be recorded on the checklists and tick marks for required points of comprehension should be recorded as instructed above. The study staff member who administers the checklist should document the outcome of the assessment in the space provided and should sign and date the checklist on the date of administration. Additional comments may be recorded on the checklist or on an informed consent cover sheet or other site-specific source document per site SOPs; however, such comments are not required.
13. The study staff member who administers the checklist should carefully review it to verify that comprehension of all required points was demonstrated and that this is documented on the checklist (i.e., all required points of comprehension should be ticked). It is recommended that a second study staff member also complete this verification because failure to document comprehension of all required points could be considered an informed consent and eligibility/enrollment violation.



**Figure 5-6**  
**Sample Informed Consent Coversheet for IMPAACT 2010**

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

## 6.0 STUDY VISITS AND PROCEDURES

Protocol Section 6 and the Schedule of Evaluations (SoE) provide comprehensive information on procedural requirements for conducting study visits. FAQs related to these requirements are provided in the remainder of this section; for ease of organization, FAQs related to procedural requirements under LoA #1 are provided in a separate table, starting on page 56. Further detailed information on performing DXA scans and administering questionnaires for this study is provided in Sections 7 and 8, respectively.

In protocol Version 2.0, instructions were added to protocol Section 6 with respect to visit windows and procedures to be followed if a scheduled visit is missed (i.e., not completed within the allowable window). In the event of a missed visit, the missed evaluations should be completed, if possible, at the next scheduled visit. For example, if the Antepartum Week 12 Visit is missed, the ALT, AST, creatinine, creatinine clearance, and HIV-1 RNA evaluations specified for that visit should be performed, if possible, at the Antepartum Week 16 Visit. Further operational guidance for conducting visits when previously-missed evaluations will be performed is as follows:

- At visits when previously-missed evaluations will be performed, the missed evaluations should be performed only once. For example, if the maternal Postpartum Week 14 Visit is missed, at the Postpartum Week 26 Visit, blood would be drawn for one set of chemistry tests (AST, ALT, creatinine, CrCl) and one HIV-1 RNA test (in addition to the blood required for the complete blood count and CD4+ cell count required at the Week 26 Visit). Similarly, one adherence questionnaire would be administered.
- At visits when previously-missed evaluations will be performed, if it is not possible to perform all missed evaluations (for example, due to allowable blood draw volumes or other considerations), evaluations that are important for monitoring participant safety and for assessing primary study outcomes should be prioritized. This would include safety related laboratory tests, HIV-1 RNA tests, and procedures required to ascertain pregnancy outcomes.

### **6-A What are the minimum qualifications for personnel who perform fetal ultrasound scans for this study?**

In general, personnel who perform fetal ultrasound scans should have sufficient training to perform ultrasound scans that meet the minimum criteria specified in protocol Section 6.13. Estimation of dating is the highest priority for the ultrasound scans performed for this study.

### **6-B We expect that some mothers will refuse to provide written informed consent for specimen storage and future research use, either for themselves or for their infants. Please clarify which specimens should not be collected from participants for whom informed consent is not provided.**

All specimens specified in the SoE should be collected for all enrolled participants. Consent for collection and use of all specimens per protocol is provided as part of the main study informed consent process for all participants.

Consent for specimen storage and future research use is applicable to specimens that are left over after all protocol-specified testing has been performed. After all protocol-specified testing has been performed, the leftover specimens of any participants for whom consent for specimen storage and future use was not provided will be destroyed.

**6-C     The protocol indicates that all Entry Visit procedures are expected to be performed on the day of enrollment. What should we do if this is not possible for a given mother?**

The protocol correctly specifies that all Entry Visit procedures are expected to be performed on the day of enrollment, and all sites are expected to put procedures in place to prepare for and accommodate this. In the rare event that this is not possible (e.g., if the mother is urgently called away from the study site), the remaining Entry Visit procedures should be completed as soon as possible, ideally within one day. All protocol requirements for the sequencing of Entry Visit procedures must still be followed; in particular, eligibility must still be confirmed (or re-confirmed) on the day of enrollment, prior to enrollment. Any Entry Visit conducted over more than one day should be documented as a protocol deviation in the mother's study chart; this documentation should include a description of the deviation and why it occurred as well as corrective and prevention actions taken in response to the deviation.

**6-D     The protocol indicates that, at the Entry Visit, blood collection must precede ingestion of the first dose of study drug. We routinely source document the time of specimen collection at all study visits. Are we required to source document the time of first study drug ingestion?**

You are correct that the protocol specifies blood collection should precede ingestion of the first dose of study drug, and source documentation recorded at the Entry Visit should substantiate compliance with this aspect of the protocol.

For a mother who takes her first dose in the evening of the Entry Visit, this should be relatively straightforward to source document, even if a specific time of first dose is not identified. In this case, source documentation for the Entry Visit would note the time of blood draw and would note that the first dose was not taken during the visit. This would be sufficient to substantiate that the blood draw occurred before the first dose. It is generally expected that you would then contact the mother on the day after the Entry Visit to confirm whether she took her first dose. You would document her response and notations such as "participant reported that she took her first dose at bedtime on the day of entry" suffice to source document the proper sequence of events.

For a mother who takes her first dose at the Entry Visit, further detailed notes may be required to source document the proper sequence of events during the visit. In this case, source documentation for the Entry Visit would note the time of blood draw. You could also note the time of first dose during the visit. A notation such as "participant took her first dose of study drug during the visit after blood draw" should also suffice to source document the proper sequence of events. We would also highlight that contemporaneous documentation during the Entry Visit would be important. For example, if a series of chart notes is entered into the mother's study record over the course of the visit, the note documenting the blood draw should come first, followed by the note documenting the first dose of study drug.

**6-E     For some of the mothers we have enrolled so far, administration of the PSQI at the Entry Visits has identified some minor sleep disturbances that we would commonly expect during pregnancy. On review of the DAIDS AE Grading Tables, these disturbances appear to fit the classification or grade 1 or grade 2 insomnia. Should we grade these for severity and enter them into the Medical History eCRF?**

Yes. These disturbances should be graded for severity and, if grade 1 or higher insomnia is identified, this should be entered into the Medical History eCRF (MHW10001).

**6-F We have enrolled a few mothers so far who had abnormal (grade 1 or higher) hemoglobin values at screening. Are we required to enter these values on the Medical History eCRF that we complete at the Entry Visit?**

For enrolled mothers with abnormal screening laboratory test results (within 28 days prior to study entry), the abnormal condition should be entered into the Medical History eCRF (MHW10001). As an example, for a mother with a grade 1 or grade 2 hemoglobin value, you might enter “decreased hemoglobin” into the eCRF with the associated severity grade.

**6-G If we understand correctly, the Targeted Pregnancy Diagnoses eCRF is completed at the Entry Visit and the Delivery Visit. Can you confirm this and explain why this form is completed twice?**

You are correct that this form (DXW10001) is completed twice, once at the Entry Visit and a second time at the Delivery Visit. The form is completed at the Entry Visit to capture any pre-existing diagnoses; it is completed again at the Delivery Visit to capture any new diagnoses identified while the mother is on-study.

- At Entry, record all conditions diagnosed in the index pregnancy before entry into the study. This would be based on all information collected up until the time of enrollment/randomization.
- At Delivery, record all conditions diagnosed in the index pregnancy after entry into the study. This would be based on all information collected from the time of enrollment/randomization through delivery and up to 14 days postpartum.

**6-H We have noted that the timeframe for performing Delivery Visits is much longer in protocol Version 2.0. Is there a reason why this change was made?**

It should first be emphasized that both protocol Version 1.0 and protocol Version 2.0 specify that Delivery Visits should be conducted **as soon as possible** after delivery. Therefore, operational procedures should be in place at each site to identify when each mother’s labor begins and when her infant has been delivered, so that the Delivery Visit can be conducted as soon as possible thereafter.

Protocol Version 1.0 specified that Delivery Visits should be conducted as soon as possible and within 14 days after delivery. Protocol Version 2.0 retains this same 14-day window as targeted and notes that conduct of Delivery Visits within this window will be closely monitored. As such, there should be no operational difference between protocol Version 1.0 and protocol Version 2.0 with respect to efforts made to conduct Delivery Visits as soon as possible and within 14 days after delivery. Sites that do not consistently complete Delivery Visits within the targeted window will be required to implement appropriate corrective actions plans; consideration may also be given to pausing accrual at such sites while correction action is taken.

In the event that a Delivery Visit cannot be conducted within 14 days after delivery, which is expected to be rare at each site, protocol Version 2.0 allows for the visit to be conducted up to 27 days after delivery. This change was made in protocol Version 2.0 to allow for the Delivery Visit to be conducted on any day up to the allowable window for the Week 6 Postpartum Visit, without incurring a protocol deviation.

**6-I** The language in protocol Section 6.4 related to specimen collection for Zika virus testing was updated in protocol Version 2.0 such that maternal and infant serum is specified to be stored at the Delivery Visit “only if mother is at risk for Zika virus infection (due to local transmission, travel, or other exposure) and maternal Zika virus infection during the current pregnancy is suspected.” We would like to confirm: if Zika virus infection is not suspected, should these samples not be collected?

Yes, that is correct. The change included in protocol Version 2.0 was meant to further clarify the original intent in protocol Version 1.0 that samples should be collected for Zika virus testing only if the mother is at risk of Zika virus infection and maternal Zika virus infection is suspected. The protocol team expects that very few participants, from only a subset of sites, will need to have these samples collected. Suspicion of maternal Zika virus infection will generally depend upon consistent epidemiologic data (residing in or traveling to a location with active Zika virus transmission, or having had sex with an individual with possible Zika virus infection), and suggestive clinical information (e.g., signs, symptoms, or fetal ultrasound or neonatal examination findings suggestive of possible Zika virus infection).

**6-J** Please clarify when samples are collected for PK testing in this study.

This study does not involve PK analyses. However, specimens will be collected for testing of ARV drug concentrations in support of exploratory objectives 2.3.5 and 2.3.6. As indicated in protocol Section 9.2.3.5 and 9.2.3.6:

- Maternal hair collected at the Delivery Visit will be tested for ARV drug concentrations as a measure of adherence to maternal ART regimens.
- Maternal hair and infant hair collected at the Delivery Visit will be tested for ARV drug concentrations as a measure of ARV transfer from mother to infant.
- Maternal plasma, maternal breast milk, and infant plasma collected at the Week 6 Postpartum Visit will be tested for ARV drug concentrations as a measure of ARV transfer from mother to infant.

**6-K** For mothers who may experience virologic failure, are there provisions in the protocol to test for ARV drug levels or ARV resistance?

Yes. The approach taken to ARV resistance testing was modified in protocol Version 2.0 (Sections 6.7, 6.18.2, and 8.3, and in the Schedule of Evaluations in Appendix I), such that resistance testing will be performed in real time for mothers with confirmed virologic failure. Samples for resistance testing will be collected and stored locally at Screening Visits and at Confirmation of Virologic Failure Visits. If virologic failure is confirmed (per protocol Section 8.3), these samples will be tested for resistance in real time, so that test results can be used to guide ARV regimen management, if applicable, in consultation with the CMC. The resistance testing should be performed at the laboratory specified in the site’s currently-approved protocol analyte list. Refer to the LPC for additional information and contact the IMPAACT 2010 Questions Group with any questions about where this testing should be performed.

**6-L We have noted that the SoE requires maternal hematology and chemistry testing at screening. Similarly, the SoE requires infant HIV NAT and CBC at delivery. If these tests have recently been performed outside of the study, and we can obtain adequate source documentation of the results, can we use these results for study purposes, rather than drawing additional blood to perform the same tests?**

The maternal screening test results that you describe can be used under certain circumstances:

- For all sites, the tests must have been performed using specimens collected within 14 days prior to study entry.
- For US sites, the tests must have been performed in a CAP- or CLIA-certified laboratory.
- For non-US sites, the tests must have been performed in a local laboratory that has been approved to perform these tests for IMPAACT 2010.

The infant Delivery Visit tests that you describe can be used under certain circumstances:

- For all sites, the tests must have been performed using specimens collected within the Delivery Visit window.
- For US sites, the tests must have been performed in a CAP- or CLIA-certified lab.
- For non-US sites, if the tests must have been performed in a local laboratory that has been approved to perform the tests for IMPAACT 2010.

**6-M We have noted that the SoE specifies limited hematology testing for mothers during pregnancy and postpartum. Given that many mothers will be anemic, should additional monitoring be done? Similarly, the SoE specifies limited hematology and chemistry testing for infants. If any HIV-infected infants are identified, should additional testing be done to monitor safety in relation to their ART regimen?**

The study SoE is not intended to address all aspects of maternal and infant clinical care. In general, it is expected that mothers and infants will receive standard of care services, beyond the evaluations specified in the protocol, outside of the study. Nonetheless, site clinicians are permitted to order additional tests if consistent with local standards of care and/or if clinically indicated for a given participant. The reason for all testing performed in addition to the testing specified in the SoE should be source documented in participant study charts. In addition, site clinicians are responsible for reviewing all test results and for taking appropriate action to document, report, and manage all results.

**6-N Based on experience in other studies, we believe there are specific requirements for the number of decimal places to be used when calculating creatinine clearance (CrCl) rates using the Cockcroft-Gault formula? Can you please advise on this?**

When using the Cockcroft-Gault formula for this study:

- Age should be entered in years as whole numbers with no decimal places (e.g., 22).
- Weight should be entered in kilograms with one decimal place (e.g., 56.7).
- Creatinine values should be entered with two decimal places (e.g., 0.97).

To facilitate calculation of CrCl rates, and documentation thereof, a calculator utility has been developed in Microsoft Excel and posted on the study-specific web page. A calculator utility is also available on the DMC portal.

**6-O We understand that laboratory test results that meet the criteria in protocol Section 7.2 should be entered into eCRFs regardless of whether the test was protocol-specified or ordered by the site investigator for clinical purposes. We would like to ask a question about this for maternal creatinine tests that may be ordered for clinical purposes. If this were to be done, would the site be expected to calculate a CrCl rate corresponding to the creatinine result, and potentially enter the CrCl rate into eCRFs? A complicating factor is that the mother's weight may not have been measured on the day of specimen collection for the test, so that part of the CrCl formula could be missing.**

It would be ideal to enter both the creatinine result and the corresponding CrCl rate into eCRFs if possible. However, if the CrCl rate was not otherwise calculated using the Cockcroft-Gault formula, and/or the mother's weight was not obtained, then the CrCl rate would be considered unavailable and therefore not required for entry into eCRFs.

**6-P The severity grading for creatinine clearance in the DAIDS Grading Table seems to be based on absolute values as well as changes from baseline. At our site, should we choose one of these methods to be used consistently for our participants?**

Please refer to protocol Version 2.0 CM #1 and guidance provided by the Protocol Team via email on 21 September 2018 for further information on this topic.

For both creatinine (Cr) and creatinine clearance (CrCl) rates, it is necessary to assess the severity grade based on both the absolute value and the change from baseline. If the two assessments do not provide the same grade, the higher of the two grades should be assigned. For example, if the absolute value falls into the Grade 1 range, but the change from baseline falls into the Grade 2 range, Grade 2 should be assigned.

See the table below for an example based upon a recent query to the CMC. For this participant:

- On 28 May, the same severity grade would be assigned based on absolute values and change from baseline (normal for Cr, normal for CrCl); these values and grades would be entered into the LBW10009 eCRF. The participant would be managed per the row in Appendix II, Table II.5, for "Estimated CrCl  $\geq 90$  mL/min OR Grade 1 creatinine" based on the absolute CrCl value.
- On 12 July and 7 August, the same severity grade would be assigned based on absolute values and change from baseline (normal for Cr, Grade 2 for CrCl); these values and grades would be entered into the LBW10009 eCRF. The participant would be managed per the row in Appendix II, Table II.5, for "Estimated CrCl  $< 90$  to 50 mL/min OR Grade 2 creatinine" based on the absolute CrCl value.
- On 11 September, different severity grades would be assigned based on absolute values and change from baseline. Grade 2 would be assigned to the Cr value of 0.92 mg/dL (corresponding to the grade of the change from with baseline) and grade 3 would be assigned to the CrCl value of 75.2 mL/min (corresponding to the grade of the change from baseline); these values and grades would be entered into the LBW10009 eCRF and the grade 3 increased CrCl would also be entered into the Adverse Events Log eCRF (ADE10002). The participant would be managed per the row in Appendix II, Table II.5, for "Estimated CrCl  $< 90$  to 50 mL/min OR Grade 2 creatinine" based on the absolute CrCl value.

As this example highlights, clinical decisions (participant management) should be based upon absolute Cr and CrCl values, rather than changes in these values from baseline.



Date (Visit)	Weight (kg)	Creatinine (mg/dL)	Grade (ULN)	Grade (change from baseline)	Creatinine Clearance (mL/min)	Grade (absolute value)	Grade (change from baseline)
30 APR (Screen)	57.6	0.68	0	NA	115.0	0	NA
28 MAY (Week 4)	58.8	0.63	0	0	126.7	0	0
12 JUL (Delivery)	53.8	0.82	0	0	89.1	2	2
07 AUG (Interim)	52.8	0.81	0	0	88.5	2	2
11 SEP (Interim)	51.4	0.92	0	2	75.2	2	3

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

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

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

**6-R We understand that the wording in protocol Section 6.16 related to charting infant growth has been modified in protocol Version 2.0, but still requires determination of weight-for-length Z scores to be assessed in relation to WHO growth standards. Our site would like to calculate numeric Z scores for infants in addition to use of growth charts. Can the protocol team provide use with utilities for this?**

The WHO has software available for downloading that can be used for this purpose. Downloads for personal computers and mobile devices are available at: [www.who.int/childgrowth/software/en/](http://www.who.int/childgrowth/software/en/).

**6-S We have another question related to the instruction in protocol Section 6.16 to assess weight-for-length Z scores in relation to WHO growth standards. Should the same standards be used for full term and preterm infants?**

WHO standards should be used for full term infants. WHO standards are not available for preterm infants; for these infants, the Protocol Team has advised that INTERGROWTH 21 standards for preterm infants should be used. Publications, charts, and calculator tools are available at: <https://intergrowth21.tghn.org/postnatal-growth-preterm-infants/>.



**6-T We understand that photos of suspected congenital anomalies will be submitted to the DMC using the File Exchange Utility. Do we also need to keep electronic copies of the photos or keep paper copies participant study charts?**

You are correct that photos will be submitted to the DMC using the File Exchange Utility. Once the files have been successfully submitted, you will receive a confirmation of each file received. A copy of this confirmation should be retained on-site. It is not necessary to keep electronic or paper copies of the photos on-site. In fact, to protect participant privacy and confidentiality, and avoid potential file mix-up, this is not recommended. Therefore, once confirmation of receipt at the DMC is received, the photos should be deleted from the device used to take the photos and from any other on-site file locations. You will still be able to access and review the photos within the File Exchange Utility at any time.

**6-U Umbilical hernia is very commonly identified in newborns and, for other IMPAACT studies, we have been instructed that this condition should be not be considered a congenital anomaly. Should this condition be considered a congenital anomaly for IMPAACT 2010?**

Umbilical hernia would not generally be considered a congenital abnormality for this study. However, consistent with the infant surface exam training video, if a very large umbilical hernia is identified, this should be considered a congenital anomaly (and source documented and entered into relevant eCRFs).

**6-V We have read FAQ 6-U and understand that umbilical hernia would not generally be considered a congenital abnormality for this study (unless the hernia is very large). We would also like to ask about elective repair of umbilical hernia. If an infant is admitted to hospital for an elective repair, would the hernia then be considered a serious adverse event for the infant?**

Upon review of guidance provided in the DAIDS EAE Manual, the Protocol Team would consider an umbilical hernia that requires an inpatient procedure for repair to meet the definition of serious.

**6-W The infant surface exam training video indicates that Mongolian spots and observations such as "stork bites" and "angel kisses" are normal and should not be recorded as congenital anomalies. How should we handle these types of exam findings in IMPAACT 2010?**

All observations from infant surface exams should be source documented. With respect to entry into eCRFs, however, these types of birth marks should not be entered into congenital anomaly eCRFs.

**6-X We have a question about procedures for HIV-infected infants (protocol Section 6.8) focusing on infants who were not breastfed. If an HIV-infected infant was not breastfed, we would not expect to collect blood for HIV NAT at Week 26 or Week 38. For HIV-infected infants who were not breastfed, we believe this means that we would not collect blood for plasma storage at Week 26 or Week 38. Is that correct?**

Yes, that is correct.

**LoA-1** We understand that “contraceptive history” must now be collected at all maternal study visits, but we are somewhat confused by this term. Can you clarify what is meant by “history” in the context of information that we need to document at screening and entry, versus information that we need to collect during antepartum and postpartum follow-up. We are especially not clear on what historical information may be required.

Please refer to LoA #1 items 29 and 30 for information on this topic; the following should be documented as part of routine contraceptive histories:

- Future fertility intentions and willingness to use effective contraception following the current pregnancy should be assessed and source documented as part of eligibility determination at Screening and Entry. It is not necessary to document use of contraception prior to the current pregnancy (unless contraception was being taken at the time of conception of the current pregnancy). For mothers enrolled under LoA #1, confirmation of future fertility intentions and willingness to use contraception consistent with inclusion criterion 4.1.8 will be entered into the SES.
- Contraception plans should be source documented during antepartum follow-up (starting at the Antepartum Week 4 visit) and finalized at the Delivery Visit (no eCRF entries are required).
- Contraception use should be source documented throughout postpartum follow-up; methods used should be entered into eCRFs as described in FAQ LoA-2, below.

**LoA-2** We understand that contraceptives used postpartum should be source documented and entered into eCRFs. Does this include male and female condoms? What eCRFs do we use for this purpose?

Most contraceptive methods, including all methods designated as effective in LoA #1, should be entered into the Concomitant Medications Log eCRF (CMW10001).

Male and female condom use should not be entered into the Concomitant Medications Log eCRF but should be indicated in Item 20 of the Study Event Tracking – Maternal eCRF (SVW10001), “At this visit or since the last visit, has the participant consistently used condoms (male or female) as a method of contraception?” If a mother reports that condoms are usually or always used, answer “yes” to this question; if a mother reports that condoms are never, rarely, or only intermittently used, answer “no” to this question.

**LoA-3** We have some mothers at our site who delivered and started using contraception before LoA #1 was implemented. Do we need to go back to their Concomitant Medications Log eCRFs and update the prior entries so that the entries are now consistent with the requirements of the LoA?

Yes; because of the importance of documenting all contraceptive methods used postpartum, prior entries for all mothers should be reviewed and updated as needed. For example, if a mother had an intrauterine contraceptive device inserted soon after delivery, before LoA #1 was implemented, the device would not have been entered into the Concomitant Medications Log eCRF previously and should now be entered. In addition, for all contraceptive methods, the indication entered into the Concomitant Medications Log eCRF should be “Contraceptive use” (which will be available in the dropdown list when the Implementation Notice for LoA #1 is issued).

**LoA-4** We would like to request assistance with entering start and stop dates for contraceptive methods in the Concomitant Medications Log eCRF. This seems clear for some methods, but not others. For example, how do we enter these data for injections, which cover a 2-3 month period, and for methods like patches and rings, which may be applied or inserted and then removed each month? Lastly, for mothers who take pills, how should we handle missed doses?

- For surgical sterilization procedures, enter the procedure date as the start date (do not enter an end date unless the procedure is surgically reversed).
- For intrauterine contraceptive devices and systems (IUDs and IUSs), enter the date of insertion as the start date and the date of removal (or expulsion) as the end date.
- For contraceptive implants, enter the date of insertion as the start date and the date of removal as the end date.
- For contraceptive injections, enter each injection as a separate entry, with the date of injection entered as the start date and the end date.
- For oral contraceptive pills, enter the date of first pill ingestion as the start date. If use of pills was (or is being) discontinued, enter the date of the last pill ingested as the end date.\*
- For contraceptive patches, enter the date of first patch application as the start date. If use of patches was (or is being) discontinued, enter the date of last patch removal as the end date.\*
- For contraceptive vaginal rings, enter the date of first ring insertion as the start date. If use of rings was (or is being) discontinued, enter the date of last ring removal as the end date.\*

*\*Note:* Any reported missed pills or early removal of a patch or ring by a participant should be source documented but these gaps in contraceptive adherence are not otherwise expected to be reflected in eCRF entries.

**LoA-5** We have noted the change made in LoA #1 that all medications taken “at the time of conception and during the current pregnancy” should be source documented and entered into eCRFs. How should we determine the date of conception, from which this required reporting should begin?

An estimated date of conception should be calculated from the best available estimated date of delivery (EDD) as of the mother’s date of enrollment into the study. To calculate the estimated date of conception, subtract 266 days from the EDD. Alternatively, an online calculator can be used for this purpose, for example:

<https://www.calculator.net/pregnancy-conception-calculator.html>.

**LoA-6** In LoA #1, Table 3 was updated to specify that all medications taken during pregnancy should be entered into eCRFs. Does this include all medications received during the intrapartum period?

No. It is not necessary to enter all medications received during the intrapartum period into eCRFs. These medications should only be entered into eCRFs if they meet other criteria for eCRF entry. For example, if a mother experiences a serious adverse event during labor, and a medication is given during the intrapartum period to treat or manage that adverse event, then the medication should be entered into eCRFs.

**LoA-7 Do we understand correctly that we are expected to provide contraception counseling at all maternal study visits, even at antepartum visits, prior to delivery?**

Yes, that is correct. The intent is to provide counseling to enable enrolled mothers to identify — while they are still pregnant — plans to initiate effective contraception after they have delivered. Plans should be documented beginning at the Antepartum Follow-Up Week 4 Visit and reviewed and updated as needed at each subsequent antepartum visit. At the Delivery Visit, plans should be finalized, and effective contraception should be initiated within the Delivery Visit window (i.e., within 27 days after delivery).

**LoA-8 We are not able to perform pregnancy testing on-site. Rather, we send urine samples to our lab, which is located off-site. Because of this, we will not generally have results back within the time it usually takes to conduct a maternal study visit. Can we continue to provide ARVs to mothers while we are waiting for their pregnancy test results to come back?**

Yes. Pregnancy test results should ideally be obtained in real-time during maternal study visits. However, it is acknowledged that this is not possible at all sites. At sites where this is not possible, results should be obtained by the next day, but it is not necessary to wait for the results to provide ARVs, unless pregnancy is suspected. Of note, any positive pregnancy test result postpartum should be handled as a critical lab value in this study.

**LoA-9 Are we required to provide contraception counseling and perform pregnancy testing for mothers who have a sterilization procedure postpartum?**

Please refer to LoA #1 item 19. For mothers who undergo documented surgical sterilization after delivery or other pregnancy outcome, contraception counseling and initiation of other contraceptive methods are not required after the sterilization procedure is performed.

Note that this exception applies for mothers with documented surgical sterilization. If adequate documentation of the sterilization cannot be obtained, contraception counseling must still be provided.

With respect to pregnancy testing, there is no exception for mothers who undergo surgical sterilization. Pregnancy testing is required at all postpartum visits for all mothers.

**LoA-10 Are we required to provide contraception counseling and perform pregnancy testing for mothers whose partners have undergone a vasectomy? How about for mothers whose partners die or who report abstinence from sexual activity for cultural reasons?**

There are no exceptions to these required procedures based on a male partner's fertility or sterility status or a mother's reported abstinence from sexual activity. Therefore, for mothers who may report these types of circumstances, the required procedures should still be performed.

**LoA-11** If we enroll a mother who states at entry that she is willing to use contraception, but then refuses to use an effective method after her baby is born, will this be considered a protocol deviation or eligibility violation?

No. It is understood that fertility intentions may change over time, and that mothers who previously reported a willingness to use contraception may change their minds after delivery. Mothers who are not willing to use contraception postpartum should remain on-study and may require modification of their ART regimen, consistent with LoA #1 items 23 and 37.

*Note:* This same answer would also apply for mothers enrolled prior to the issuance of LoA #1; if any such mother is not willing to use contraception postpartum, this would not be considered a protocol deviation.

**LoA-12** We understand that mothers taking DTG who are not willing to use effective contraception postpartum should be switched off DTG. Can these mothers be given other study-supplied ARVs, or do they need to obtain their ARVs from non-study sources?

Both of these options are acceptable. For ease of access and to assure consistent availability, on-site provision of study-supplied ARVs is preferred. However, non-study supplied ARVs may be provided. All ARV regimen changes should be made in consultation with the CMC, and communications with the CMC should note the proposed source of ARVs to be provided.

**LoA-13** We understand that mothers taking DTG who are not willing to use effective contraception postpartum should be switched off DTG. Should mothers who are only willing to take oral contraceptive pills also be switched off DTG?

Long acting reversible contraceptive (LARC) methods or injectable hormonal methods should be strongly recommended to all enrolled mothers and site staff should actively facilitate access to such methods. For mothers who are not willing or able to use LARC or injectable hormonal methods, use of other methods designated as effective in LoA #1 is acceptable, and use of these methods does not require a switch off DTG. For mothers who choose to use oral contraceptive pills, ongoing counseling should be provided to support adherence to daily pill taking and to continue to offer injectable hormonal and LARC methods over time.

In the event that staff at your site become concerned that a mother is not adhering well to her chosen method of contraceptive, consideration may be given to recommending switch off of DTG, in consultation with the CMC.

**LoA-14** We understand that mothers taking DTG who are not willing to use effective contraception postpartum should be switched off DTG. What management should we follow for mothers who wish to stay on DTG and are able to access DTG from non-study sources? Should we discontinue any such mother from the study?

No. Any such mother should ideally stay on-study as originally planned (through Week 50 postpartum) regardless of her ARV choices. The mother should be informed of her ARV and contraception options and counseled on the potential risks and benefits of her choices. All counseling discussions and the mother's choices should be source documented.

**LoA-15 We understand that mothers taking DTG who are not willing to use effective contraception postpartum should be switched off DTG. What management should we follow for mothers taking EFV who are not willing to use effective contraception postpartum?**

You should continue to provide contraception counseling to these mothers and to perform pregnancy testing per the Schedule of Evaluations provided in LoA #1. There are no specifications in LoA #1 that would require a change of ART regimen for these mothers.

**LoA-16 We will soon have mothers who complete their study participation at Week 50 postpartum. How should we counsel mothers who are taking DTG, if they have the option of staying on DTG post-study?**

Per protocol Sections 6.5.4 and 6.5.5, discussions of transition to non-study care and treatment should occur at Weeks 38 and 50 postpartum, with information, counseling, and/or referrals provided as needed. Study drug cannot be dispensed to mothers at or after the Week 50 Visit; therefore, operational plans must be in place to permit transition to non-study care and treatment at this visit.

For mothers on DTG who have the option to stay on DTG post-study, transition discussions should provide any available updates on the potential risks and benefits of DTG and should take into consideration the mother's future fertility intentions and post-study contraception options. Counseling should also reflect local standards of care and current HIV treatment guidelines. Referrals should be provided, as needed, for both HIV care and treatment and contraceptive services. The mother's ARV and contraceptive choices should be source documented, and follow-up should occur at the post-study contact described in protocol Section 6.10.

**LoA-17 We have some concerns about initiation of hormonal contraceptive methods in relation to breast milk production and the importance of breastfeeding for infant health in our setting. Can you provide more information on preferred contraceptive methods for breastfeeding mothers?**

Phillips et al conducted a systematic literature review for the WHO's Medical Eligibility Criteria for Contraceptive Use and examined the effects of progestogen-only contraceptives (including progestogen-only pills, injectables, implants, or IUDs) on outcomes such as breastfeeding performance and infant growth, development, and health, and concluded that the overall evidence does not show adverse breastfeeding outcomes or negative health outcomes in infants such as restricted growth, health problems or impaired development (Contraception 2016). See Figure 10-1 (on page 85) for further study-specific guidance on preferred contraceptive methods during the first 27 days after delivery. Of note, use of "bridging" methods in the first 27 days may be clinically indicated in some settings if additional time is needed for women to initiate their preferred methods (see also FAQ LoA-18).

All study sites are encouraged to follow local standard guidelines for providing contraception to breastfeeding women with HIV infection. Please contact the CMC with any questions that may arise, especially for cases in which local guidelines do not recommend an effective contraceptive method that the participant is willing to use.



**LoA-18** We have some concerns about the requirement in LoA #1 that mothers start effective contraception within 27 days after delivery. We do not generally expect to attend the deliveries of most of our enrolled participants, so we may not be able to ensure initiation of methods such as IUDs within 48 hours of birth. In addition, there are some methods that our local standard guidelines do not recommend starting within 27 days. Can you provide further guidance in relation to these issues?

It is understood that study staff may not attend participant deliveries and therefore may not be in a position to help ensure initiation of contraception soon after delivery. It is also understood that study staff should manage participants consistent with local standard of care. Therefore, the Protocol Team would generally not recommend deviation from local standard guidelines for study participants. See Figure 10-1 (on page 85) for further study-specific guidance on preferred contraceptive methods during the first 27 days after delivery.

For any participant who cannot initiate her preferred method within the first 27 days after delivery, the team recommends that the preferred method be initiated as soon as feasible. During the intervening period before the preferred method can be initiated, the participant should use a “bridging” method such as progestogen-only pills or injections. As long as the bridging method is considered an effective method per LoA #1, and is started within 27 days after the delivery, the participant will be considered in compliance with the protocol specification to initiate effective contraception within 27 days.

**LoA-19** We see in LoA #1, item 37, that sites should offer a fetal ultrasound between 14 and 22 weeks gestation for mothers experience a subsequent pregnancy during postpartum follow-up. Should this be done even if the mother completes her study participation (through 50 weeks) before she reaches 14 weeks gestation in the new pregnancy? Are there any special considerations for us to note related to this?

You are correct that LoA #1 specifies that sites should offer a fetal ultrasound scan to any mother who experiences a subsequent pregnancy during postpartum follow-up. This scan can be offered between 14 and 22 weeks gestation but ideally should be performed between 18 and 22 weeks gestation to allow for better visualization of fetal anatomy. The scan should be offered even if the targeted timeframe falls after the mother’s Week 50 Visit.

The ultrasound scan should be used to confirm the dating of the pregnancy and to evaluate fetal anatomy. It should ideally be performed by an ultrasonographer with experience in assessing fetal anatomy (e.g., Level 2 US). Results should be source documented and entered into the IMPAACT 2010 Last Menstrual Period and Ultrasound Information eCRF (EVW10012), consistent with protocol Table 3.

NIAID sites can submit for reimbursement of the costs of these ultrasound scans to the IMPAACT Finance Group. NICHD should contact Westat.

## **7.0 PERFORMING DXA SCANS**

At selected sites, mothers will undergo DXA scans of the lumbar spine and hip at Week 50 postpartum and infants will undergo DXA scans of the whole body and lumbar spine at Week 26 postpartum. DXA scans will be performed according to standardized procedures that will be adapted from procedures followed in the IMPAACT P1084s sub-study of PROMISE. These procedures will be described in a separate manual that will be posted on the study-specific web page when available.

DXA scan images will be transmitted electronically in real time for centralized reading and subsequently transmitted electronically from the central readers to the DMC. Study sites are not expected or required to maintain hard copies in participant study records.

The centralized readings of all scans will be made available to the study sites after the last scan has been read centrally. However, if an infant experiences a bone fracture subsequent to his or her scan, the result of his or her scan will be provided to the site as soon as available.



## 8.0 ADMINISTERING STUDY-SPECIFIC QUESTIONNAIRES

Six study-specific questionnaires will be administered to mothers enrolled in this study:

- QLW10001: Routine Adherence Assessment
- QLW10007: Facilitators of Adherence
- QLW10004: Barriers to Adherence
- QLW10000: Edinburgh Postnatal Depression Scale
- QLW10006: Generalized Anxiety Disorder 7-Item Scale
- QLW10005: Pittsburgh Sleep Quality Index

Each questionnaire will be interviewer-administered using paper-based forms (source documents) and data collected will be entered into eCRFs. To standardize this interviewer-administered data collection from site to site, and to maximize data quality, questionnaires must be administered in a non-biased, non-judgmental manner. Study staff should help participants feel comfortable sharing their personal information and opinions while asking questions in a consistent manner from participant to participant.

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

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

The remainder of this section provides general guidance for administering all interviewer-administered questionnaires as well as specific detailed instructions for each questionnaire.

### 8.1 General Guidance for Questionnaire Administration

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

#### 8.1.1 Welcoming the Participant

When a participant decides to take part in a study, everything about the study is new. Help make her feel comfortable. Similarly, when a new questionnaire is introduced later in follow-up, help make the participant feel comfortable with questions that have not been asked before.

- Considering offering the participant a cup of tea or other refreshment.
- Introduce yourself and try to create rapport (connection) between yourself and the participant to help her feel comfortable during administration of the questionnaire.

- Speak with the participant and administer questionnaires in the participant's preferred language. Choose the local language questionnaire that corresponds to the participant's preferred language and read directly from that form. **Do not** use another language form and translate in real-time.
- If considered helpful, offer the participant a blank copy of the form (in the preferred language) to read along as the questionnaire is administered. It is also acceptable for the participant to see the copy of the questionnaire being completed by the interviewer, as responses are being recorded, because this can reduce anxiety and increase collaboration.
- Some questionnaires include introductory statements to help prepare the participant for sensitive questions. Read these introductions as they appear on the forms.

### 8.1.2 Asking Sensitive Questions

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

### 8.1.3 Pacing the Questions

Every participant is different. Some will answer questions quickly. Others may take longer to answer or may change their answers after giving more thought to the question. Always account for this variety when administering questionnaires. Read questions slowly and let the participant finish thinking before you record her answer and go on to the next question.

### 8.1.4 Reading Items Aloud

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

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

For questions with multiple sub-parts, read all sub-parts to the participant and mark the appropriate response for each, based on the participant's answers.

### 8.1.5 Recording Participant Responses Verbatim

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

### 8.1.6 Probing

One of the objectives of the study questionnaires is to obtain accurate information on participant behaviors (e.g., adherence), feelings, and opinions. The questionnaires ask participants to recall information that participants may not have thought about or may have difficulty remembering. The technique for helping a participant remember an answer, clarify a response, decide between two similar but different answers, or report something more precisely is called **probing**.

Effective probing helps a participant think more about a question or refine an answer that is too general. However, probing must not bias or otherwise direct participant answers. As the interviewer, you cannot offer an answer to the participant. Therefore, all probes must be neutral.

The following are some probing strategies to use when a participant initially answers “don't know” to a question or cannot remember or refine her response enough to answer the question.

- **Repeat Probe:** The repeat probe is used by repeating the item or response categories. Although the participant might hear you the first time you ask a question, she may need to hear the question more than once to provide an answer. Instead of rephrasing a question, always first repeat the question as written. Sometimes hearing the question a second time is all that is needed.
- **Echo Probe:** The echo probe involves repeating the participant's exact response. Sometimes hearing the answer with a different voice will help her be more precise. The echo should always be repeated in a neutral, non-judgmental style.
- **Silent Probe:** The silent probe is used by pausing briefly after a participant gives what seems to be an uncertain answer. Although silence can feel awkward, sometimes it is helpful when a participant is trying to determine the most accurate answer to a question. Use a silent probe when the participant sounds unsure of her answer and may need some extra time to think more carefully about the question.
- **Non-verbal Probe:** The non-verbal probe is used by giving hand or facial gestures that may help the participant to come up with an answer. All such gestures must be neutral and non-judgmental.
- **Specification Probe:** The specification probe is used by asking the participant to give a more precise answer. Although a participant may give an answer that he or she considers accurate, it may not be specific enough. For example, if an item asks how many times the participant did something and she answers with a range (“5 to 10”). If a more precise answer is needed for the question, the probe, “Can you be more specific?” is often enough to help the participant choose the most accurate response.
- **Historical Probe:** The historical probe is used by asking whether the event in question occurred anytime around major holidays or personal events such as a birthday or other life event. Some items require the participant to recall dates, and initially she may be unable to recall a date. Referencing a calendar can also help the participant remember dates.

### 8.1.7 Watching for Non-Verbal Cues

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

### **8.1.8 Checking Your Work**

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

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

## 8.2 Specific Guidance for Routine Adherence Assessment (QLW10001)

*This questionnaire must be administered by a study staff member who is not involved in providing ARV adherence counseling to participants.*

*This questionnaire should be administered at all scheduled antepartum and postpartum follow-up visits before provision of adherence counseling at these visits.*

- Read the introductory statement at the beginning of the questionnaire.
- For item 2, read the question to the participant word-for-word. Allow the participant to then report the number of days (in the last 30 days) on which a dose of ARVs was missed. If needed, use probes to assist the participant in identifying her best estimate of the number of days.
- For items 3 and 4, read the question to the participant word-for-word; after reading each question, read the response categories word-for word. Further guidance related to these items is as follows:
  - In item 3, the emphasis is on **how good a job** the participant feels she did in taking her ARVs in the way she was supposed to. There is not a single definition of what the response options for this item will mean to different participants. Different participants may understand this item and the response options differently, and that is okay. If a participant asks for clarification, study staff may offer, “How well do you think you did at taking your ARVs as instructed? It is up to you to choose one of the answers, and there is no one meaning of any answer that is the same for everyone. What one person thinks is good or fair or poor for them may be different from what you think for yourself. That is okay. You can choose the answer that feels best for you.”
  - In item 4, the emphasis is on **how often** the participant feels she took her ARVs in the way she was supposed to. If the participant asks for clarification, study staff may offer, “The last question asked about how you did in general. This question asks about how often, or how much of the time, you took your ARVs as instructed. Of the doses you were supposed to take, how often did you take them?”
- As needed, repeat questions and/or response categories (repeat probe) to help the participant understand the question and the response categories she is asked to choose from. If needed, other types of probes may also be used to help the participant choose the response category that best matches her experience taking ARVs in the last 30 days.
- For item 5, show the participant the visual scale (on a separate card or sheet of paper, with the item text printed in the participant’s preferred language) and read the item to the participant word-for-word. Explain the visual scale as needed and ask the participant to use her finger to indicate her answer to the question on the scale. Key points to explain the scale are as follows:
  - The scale starts at 0 and ends at 100.
  - 0 means you have taken no ARVs in the last 30 days.
  - 100 means you have taken every dose of your ARVs in the last 30 days, but we know that people cannot always take all of their doses.
  - About 50 (half-way or mid-point) means you have taken about half of your ARVs in the last 30 days.

The participant is asked to point to the place on the line that shows her best assessment of how much of her ARVs she has taken in the last 30 days. After the participant indicates her answer on the line, record the number that corresponds to her answer on the questionnaire form.

- After administering all items, **retain the completed questionnaire form separate from the participant's main study file**. The questionnaire data will need to be entered into the QLW10001 eCRF but the completed questionnaire form **should not be shared** with other members of the study staff team, particularly staff members who provide adherence counseling to the participant.

The reason for this approach is to promote open responding by participants. If a participant believes her information will be shared with her care team (clinicians, counselors, pharmacists, and others who provide care, counseling, and support), she may be less likely to report problems with adherence. Reporting non-adherence to care teams can be intimidating and some people avoid it. If we can help participants understand that responses to this questionnaire are kept private, we may be able to collect data about non-adherence that may not otherwise be reported. While we will make every effort to keep these data private, there are situations in which sharing information may be warranted, as described below.

- At the Antepartum Week 8 and Postpartum Week 38 visits, perform this last step after administering all adherence questionnaire forms (QLW10001, QLW10004, and QLW10007). At all other visits, perform this last step after completing only this form (QLW10001).

After administering all items, review the questionnaire form (QLW10001) to determine whether the participant's responses indicate **extreme** non-adherence based on any of the following:

- Item 2 = more than 14 days
- Item 3 = very poor
- Item 4 = rarely or never
- Item 5 = less than 25

If **extreme** non-adherence is reported, ask the participant for permission to assist her in obtaining additional support from the care team and document whether the participant accepts or declines this assistance. Suggested wording, which may be adapted for use at each site, is as follows:

“As I mentioned earlier, my job is to ask these questions and collect your answers, and to keep your answers private. You reported some trouble with taking ARVs in the last month, and maybe you are already planning to talk to the [clinician/counselor/pharmacist] about that. Many people I have worked with have said it can sometimes be difficult to talk about trouble with taking ARVs with the [clinician/counselor/pharmacist]. If the information you have given to me today is of concern to you, or if you want to share this information with the [clinician/counselor/pharmacist], I can help. If you want, I can make sure you are able to talk with the [clinician/counselor/pharmacist], who are here to help. I can join you with the [clinician/counselor/pharmacist] or I can pass on information to them, if you give me permission to do so. If you would rather this remain private (only between you and me), that is your choice, and I will respect that. What would you like to do?”

- If the participant states that she is concerned and/or would like to have her responses shared, accept her response and proceed based on her stated wishes.
- If the participant states that she is not concerned or otherwise does not want her responses shared, accept her response and take no further action. However, you may offer assistance should she change her mind at any time.

Record on the questionnaire form whether the participant accepted or declined the offer of assistance communication support with other study staff designated to provide adherence counseling and support.

*Note:* The suggested wording above has six key components that can be conveyed in a number of different ways but should all be included in the follow-up discussion with participants who report extreme non-adherence:

- (1) You **remind** the participant that her answers are **private**.
- (2) You **acknowledge** that she is telling you about having **challenges** in the past month.
- (3) You **do not assume** that she is **planning to hide** this information from the care team.
- (4) You tell her it is **not uncommon** for people to get anxious or otherwise have difficulty reporting non-adherence to the care team.
- (5) You **offer help**.
- (6) You **accept her response**.

Even if the participant declines your offer of help, she will still receive client-centered ARV adherence counseling as described in Section 10.6 of this manual. As part of this counseling, participants will have opportunities to report adherence challenges to study staff members designated to provide adherence counseling. These staff members will also have access to information on the participant's HIV viral load, which provides an objective measure of her adherence.

### 8.3 Specific Guidance for Barriers of Adherence Questionnaire (QLW10004)

*This questionnaire must be administered by a study staff member who is not involved in providing ARV adherence counseling to participants.*

*This questionnaire should be administered at the Antepartum Week 8 and Postpartum Week 38 Visits before provision of adherence counseling at these visits. This form should also be administered after the QLW10001 (Routine Adherence) form and before the QLW10007 (Facilitators of Adherence) form.*

- Read the appropriate introductory statement at the beginning of the questionnaire (Antepartum Week 8 or Postpartum Week 38).
- Then read sub-items 2a-2w to the participant word-for-word. Record “yes” if the participant indicates that a sub-item created difficulty in taking her ARVs during the referenced time period. Record “no” if the participant indicates that the sub-item did not create difficulty in taking her ARVs during the referenced time period. If the participant declines to answer, that response may be recorded.
- For sub-item 2x, ask the participant if there was any other factor that created difficulty in taking her ARVs during the referenced time period.
  - If the participant identifies any “other” factor that created difficulty, record “yes” for this sub-item and record the participant’s response verbatim in her preferred language. *After completing all questions*, translate the participant’s verbatim response into English.
  - If the participant does not identify any “other” factor that created difficulty, record “no” for this sub-item.
- For participants who do not report at least one factor that created difficulty in taking their ARVs, (as part of item 2), item 3 should be skipped.

For all other participants, read item 3 word-for-word. Repeat the question if needed or otherwise explain that the participant is asked to choose the one main factor, of all the factors discussed, that created difficulty in taking her ARVs. If the participant is not able to immediately choose one main factor, re-read the factors that she identified as creating difficulty (which should now be indicated with “yes” responses in item 2) for her to choose from. Then record for the one main factor identified by the participant in item 3.

*Note:* If “other” is selected in item 3, the description of the other factor recorded in item 3 should match with another factor recorded in item 2x.

- After administering all items, **retain the completed questionnaire separate from the participant’s main study file**. The questionnaire data will need to be entered into the QLW10004 eCRF but these data **should not be shared or discussed** with other members of the study staff team, particularly staff members who provide adherence counseling to the participant.



## 8.4 Specific Guidance for Facilitators of Adherence Questionnaire (QLW10007)

*This questionnaire must be administered by a study staff member who is not involved in providing ARV adherence counseling to participants*

*This questionnaire should be administered at the Antepartum Week 8 and Postpartum Week 38 Visits before provision of adherence counseling at these visits. This form should also be administered after the QLW10001 (Routine Adherence) and QLW10004 (Barriers of Adherence) forms.*

- Read the appropriate introductory statement at the beginning of the questionnaire (Antepartum Week 8 or Postpartum Week 38).
- Then read sub-items 2a-2q to the participant word-for-word. Record “yes” if the participant indicates that a sub-item helped her take her ARVs during the referenced time period. Record “no” if the participant indicates that a sub-item did not help her take her ARVs during the referenced time period. If the participant declines to answer, that response may be recorded.
- For sub-item 2r, ask the participant if there was any other factor that helped her take her ARVs during the referenced time period.
  - If the participant identifies an “other” factor that helped, record “yes” for this sub-item and record the participant’s response verbatim in her preferred language. *After completing all questions*, translate the participant’s verbatim response into English.
  - If the participant does not identify an “other” factor that helped, record “no” for this sub-item.
- For participants who do not report at least one factor that helped in taking their ARVs (as part of item 2), item 3 should be skipped.

For all other participants, read item 3 word-for-word. Repeat the question if needed or otherwise explain that the participant is asked to choose the one main factor, of all the factors discussed, that made it easier for her to take her ARVs. If the participant is not able to immediately choose one main factor, re-read the factors that she identified as helpful (which should now be indicated with “yes” responses in item 2) for her to choose from. Then record the one main factor identified by the participant in item 3.

*Note:* If “other” is selected in item 3, the description of the other factor recorded in item 3 should match with another factor recorded in item 2r.

- After administering all items, **retain the completed questionnaire separate from the participant’s main study file**. The questionnaire data will need to be entered into the QLW10007 eCRF but these data **should not be shared or discussed** with other members of the study staff team, particularly staff members who provide adherence counseling to the participant.

#### 8.4.1 FAQs Related to Adherence Questionnaires (QLW10001, QLW10004, QLW10007)

- 8-A We understand that study staff who administer adherence questionnaires should not provide adherence counseling to participants. We have two questions related to this:**
- **Do we need to document staff roles and responsibilities in relation to the adherence questionnaires and adherence counseling on our delegation of duties log?**
  - **Can completed adherence questionnaires be shared with other study staff who do not administer these questionnaires?**

The answer the first question is yes: Each's site's delegation of duties log should indicate which study staff will administer adherence questionnaires and which study staff will provide adherence counseling.

The answer to the second question is no: Completed adherence questionnaire forms should not be shared with other study staff who do not administer the questionnaires. Each site should establish a filing system for storing the completed questionnaires separate from the remainder of the participant study file. This approach will be taken in this study to encourage honest and accurate reporting of adherence data. See Section 8.2 of this manual for more information.

- 8-B We understand that the adherence barriers and facilitators questionnaires will be administered at Antepartum Week 8 and Postpartum Week 38. We have three questions related to this:**
- **Should the routine adherence questionnaire also be administered at these visits?**
  - **Should these questionnaires be administered by the same staff who administer the routine adherence questionnaire?**
  - **In which order should the questionnaires be administered?**

All three of these questionnaires — routine adherence (QLW10001), barriers to adherence (QLW10004), and facilitators of adherence (QLW10007) — should be administered at the Antepartum Week 8 and Postpartum Week 38 Visits. The same study staff member should administer all three questionnaires in the following order: routine adherence, then barriers, then facilitators.

- 8-C What should interviewers do if participant responses to the visual scale question on the routine adherence questionnaire do not match with other responses on this questionnaire?**

Interviewers may repeat or clarify any questions that a participant does not appear to understand. However, it is not expected that participant responses to the four questions on the routine adherence questionnaire will always match. For example, a participant may report few missed doses or rate her adherence as excellent, and then point to a lower number of the visual scale. The opposite may also occur. These types of “discrepancies” are expected and acceptable because different questions ask about adherence in different ways, and may elicit different responses. In addition, when responses to different questions do not match, it is not possible to know which responses best reflect a participant's actual adherence. For these reasons, it is not expected that interviewers will seek consistency across questions or take other action when responses to different questions do not match.

## 8.5 Specific Guidance for Edinburgh Postnatal Depression Scale (EPDS) (QLW10000)

*This questionnaire is administered at the Postpartum Week 6 and Postpartum Week 50 Visits. It may be administered by any study staff member who has been trained in questionnaire administration and associated site SOPs as referenced below.*

- Read the introductory statement at the beginning of the questionnaire, highlighting that the questions on this form ask about how the participant has felt over the course of the past seven days.
- Read each numbered statement (1-10) to the participant word-for-word; after reading each statement, read the response categories for that statement word-for word. Note that the response categories differ for each statement.
- As needed, repeat the numbered statements and/or response categories (repeat probe) to help the participant understand the statements and the response categories she is asked to choose from. If needed, other types of probes may also be used to help the participant choose the response category that best matches how she has felt in the past seven days.
- Do not read the last item on the form (regarding referral) to the participant. Record “yes” or “no” for this item based on whether referrals were subsequently made. “Yes” should be recorded whenever referrals to relevant services or resources available within the study site or external to the study site. All referrals should be further source documented in participant study records consistent with guidance provided in Section 10 of this manual.
- For this study, the EPDS is not intended to be — and should not be — used for diagnostic purposes or to make decisions regarding study drug changes. As such, there is no expectation or requirement that questionnaire responses will be numerically scored. However, questionnaire responses may prompt further action with respect to potential neuropsychiatric problems.

*After all questionnaire items are administered, follow site-specific SOPs with respect to further evaluation, treatment, documentation, and/or reporting of reported symptoms of depression.*

*Separate from questionnaire administration, a designated study staff member should discuss reported symptoms with the participant as needed to determine the following:*

- Whether the participant may require additional support, evaluations, and/or treatment for possible depression or other mental health issues (see Section 10.5 of this manual for further guidance on expectations for mental health counseling and referrals)
- Whether the participant may have experienced a Grade 1 or higher condition based on the DAIDS Toxicity Tables
- Whether any conditions meeting criteria for entry into Adverse Event eCRFs have occurred

*Note:* It is not generally expected that there will be a one-to-one correspondence between questionnaire responses and entries into Adverse Event eCRFs; clinical judgement is required to determine whether a participant has experienced an adverse event and whether any such adverse event meets protocol criteria for entry into Adverse Event eCRFs.

## 8.6 Form-Specific Guidance for Generalized Anxiety Disorder 7-Item Scale (GAD-7) (QLW10006)

*This questionnaire is administered at the Entry, Antepartum Week 8, and Postpartum Week 38 Visits. It may be administered by any study staff member who has been trained in questionnaire administration and associated site SOPs as referenced below.*

- Read the leading question in item 2 to the participant word-for-word, highlighting that the questions on this form ask about how the participant has felt over the course of the last two weeks.

Then read each sub-item (2a-2g) to the participant word-for-word; after reading each item, read the response categories word-for word. Note that the response categories are the same for all sub-items.

- As needed, repeat the leading question, sub-items, and/or response categories (repeat probe) to help the participant understand the sub-items and the response categories she is asked to choose from. If needed, other types of probes may also be used to help the participant choose the response category that best matches how she has felt in the last two weeks.
- For participants who respond “not at all” to all sub-items in item 2, item 3 should be skipped.

For all other participants, read item 3 word-for-word and then read the response categories word-for-word. Use probes as needed to help the participant choose the response category that best matches her experience in the last two weeks.

- Do not read item 4 (regarding referral) to the participant. Record “yes” or “no” for this item based on whether referrals were subsequently made. “Yes” should be recorded whenever referrals to relevant services or resources available within the study site or external to the study site. All referrals should be further source documented in participant study records consistent with guidance provided in Section 10 of this manual.
- For this study, the GAD-7 is not intended to be — and should not be — used for diagnostic purposes or to make decisions regarding study drug changes. As such, there is no expectation or requirement that questionnaire responses will be numerically scored. However, questionnaire responses may prompt further action with respect to potential neuropsychiatric problems.

*After all questionnaire items are administered, follow site-specific SOPs with respect to further evaluation, treatment, documentation, and/or reporting of potential symptoms of anxiety.*

*Separate from questionnaire administration, a designated study staff member should discuss reported symptoms with the participant as needed to determine the following:*

- Whether the participant may require additional support, evaluations, and/or treatment for possible anxiety or other mental health issues (see Section 10.5 of this manual for further guidance on expectations for mental health counseling and referrals)
- Whether the participant may have experienced a Grade 1 or higher condition based on the DAIDS Toxicity Tables
- Whether any conditions meeting criteria for entry into Adverse Event eCRFs have occurred

*Note:* It is not generally expected that there will be a one-to-one correspondence between questionnaire responses and entries into Adverse Event eCRFs; clinical judgment is required to determine whether a participant has experienced an adverse event and whether any such adverse event meets protocol criteria for entry into Adverse Event eCRFs.

## 8.7 Form-Specific Guidance for Pittsburgh Sleep Quality Index (PSQI) (QLW10005)

*This questionnaire is administered at the Entry, Antepartum Week 8, and Postpartum Week 38 Visits. It may be administered by any study staff member who has been trained in questionnaire administration and associated site SOPs as referenced below.*

- Read the introductory statement at the beginning of the questionnaire, highlighting that the questions on this form ask about usual sleep habits for the majority of days and nights in the past month.
- For items 2-5, read the questions word-for-word and record the participant's response. Repeat the questions and/or use probes as needed to help the participant provide the most accurate responses for the past month.
- For item 6, read the introductory statement, highlighting that the next several items ask about trouble sleeping in the past month. Then read each sub-item (6a-i) to the participant word-for-word; after each sub-item, read the response categories word-for word. Note that the response categories are the same for all sub-items.
- As needed, repeat the leading question, sub-items, and/or response categories (repeat probe) to help the participant understand the sub-items and the response categories she is asked to choose from. If needed, other types of probes may be used to help the participant choose the response category that best matches her sleep habits in the past month.
- For sub-item 6j, ask the participant if she experienced any other cause of trouble sleeping in the past month.
  - If the participant identifies any “other” cause, record the cause verbatim in the participant's preferred language. Then ask how often the participant had trouble sleeping because of this cause and read the response categories word-for-word. *After completing all questions*, translate the participant's verbatim response into English.
  - If the participant does not identify an “other” cause, record “not during the past month” for this item.
- For items 7-10, read the questions and response categories to the participant word-for-word. As needed, repeat the questions and/or response categories (repeat probe) to help the participant understand the questions and the response categories she is asked to choose from. If needed, other types of probes may also be used to help the participant choose the response category that best matches her experience in the past month.
- For this study, the PSQI is not intended to be — and should not be — used for diagnostic purposes or to make decisions regarding study drug changes. As such, there is no expectation or requirement that questionnaire responses will be numerically scored. However, questionnaire responses may prompt further action with respect to potential neuropsychiatric problems.

*After all questionnaire items are administered*, follow site-specific SOPs with respect to further evaluation, treatment, documentation, and/or reporting of potential symptoms of insomnia or other sleep disturbance.

*Separate from questionnaire administration*, a designated study staff member should discuss reported symptoms with the participant as needed to determine the following:

- Whether the participant may require additional support, evaluations, and/or treatment for possible insomnia, other sleep disturbance, or other mental health issues (see Section 10.5 of this manual for further guidance on expectations for mental health counseling and referrals).
- Whether the participant may have experienced a Grade 1 or higher condition based on the DAIDS Toxicity Tables
- Whether any conditions meeting criteria for entry into Adverse Event eCRFs have occurred

*Note:* It is not generally expected that there will be a one-to-one correspondence between questionnaire responses and entries into Adverse Event eCRFs; clinical judgment is required to determine whether a participant has experienced an adverse event and whether any such adverse event meets protocol criteria for entry into Adverse Event eCRFs.

## 9.0 PHARMACY CONSIDERATIONS

Refer to protocol Section 5 for detailed information regarding maternal study drug regimens, study drug supply, and study drug accountability. Protocol Section 5 also provides information on maternal and infant concomitant medications; listings of precautionary and prohibited medications can be found on the study-specific web page:

<http://impaactnetwork.org/studies/IMPAACT2010.asp>

General and visit-specific guidance on prescribing and dispensing maternal ARVs for this study is provided in Sections 9.1 and 9.2; guidance related to concomitant medications is provided in Section 9.3; and FAQs are provided in Section 9.4.

In protocol Version 2.0, Section 5.4 was revised to permit use of non-study supplies of study drug (i.e., supplies of DTG, FTC/TAF, FTC/TDF, or EFV/FTC/TDF obtained from non-study sources), with approval in advance from the CMC. It is generally not expected that non-study supplies of study drug will be needed. However, in the event that study supplies become unavailable, protocol Version 2.0 would allow for use of non-study drug supplies. Should the Protocol Team become aware of a potential need for use of non-study drug supplies, study sites will be notified. Likewise, any site that becomes aware of a potential need for use of non-study drug supplies should immediately notify the CMC. No non-study supplies of study drug should be provided to study participants without consultation in advance with the CMC.

### 9.1 General Prescribing and Dispensing Guidance

- All sites must establish SOPs for prescribing and dispensing ARVs in this study. Clinic and pharmacy staff should work together on these SOPs to specify (in advance of study initiation) the most appropriate site-specific procedures to be followed. After study initiation, site SOPs may be updated as needed to reflect actual experiences and lessons learned in the early stages of study implementation.
- Site SOPs must specify that unused tablets brought back to the clinic by a given mother can be returned to that mother, if assessed as in good condition by the pharmacist.
- ARVs may be dispensed for in-home or in-hospital delivery to mothers. Sites wishing to do this should specify procedures in their SOPs and adapt chain of custody logs to adequately document this type of dispensing.
- There is no required format for ARV prescriptions for this study. It is recommended that the mother's estimated date of delivery be recorded on the prescription.
- At any study visit, the quantity of ARVs dispensed may be determined collaboratively by the site clinician and pharmacist, based on the needs of the mother. Consensus-building discussion during the IMPAACT Annual Meeting in June 2017 identified the following:
  - Some sites may choose to dispense only a 30-day supply and to schedule additional “pharmacy only” visits for purposes of ARV dispensing in between protocol-specified visits. Sites taking this approach noted that, in their experience, mothers may not return on time for visits if they have excess ARV supplies in their possession. With this approach, the site clinician may prescribe a 90-day supply, whereas the pharmacist would dispense only 30 of the 90 days at a time.
  - Other sites may choose to dispense larger quantities to cover through the allowable window of the next protocol-specified visit.

- Most sites expressed some discomfort with dispensing more than a 90-day supply. Although this approach would be permitted per protocol, sites would generally prefer to utilize the visit windows to have women come back a little early in the window rather than dispense more than a 90-day supply.
- At all sites, SOPs should include adequate provisions to minimize missed ARV doses due to running out of supplies between visits. Special care should be taken to providing adequate supplies to leading up to and immediately following delivery.

## 9.2 Visit-Specific Dispensing Guidance

- **Entry Visit:** Dispense 30-day or 60-day supply at site discretion. Remind mother to bring all bottles and unused tablets to all visits. Following the Entry Visit, throughout follow-up, unused tablets may be returned to mothers at subsequent visits if in good condition (as assessed by the pharmacist).
- Per protocol Section 6.3, “Between scheduled visits, particularly in the first month of study participation, study site staff are encouraged to contact mothers to address any issues or questions about their study participation, clarify instructions for use of study drugs, and/or provide adherence counseling as needed.” Site SOPs should describe site-specific approaches in response to this protocol specification and site prescribing and dispensing practices should reflect these approaches.
- **Antepartum Q4 Week Visits:** Dispense 30-day supply at each visit; consider dispensing an additional 30-day “buffer” supply as mother approaches her date of delivery. Remind mother to keep taking her study-supplied tablets through labor and delivery and the protocol-specified Delivery Visit.
- **Delivery Visit:** Dispense a supply sufficient to cover through the Postpartum Week 6 visit ( $\pm 2$  weeks), including any returns the mother may still have in her possession from prior to delivery.
- **Postpartum Week 6 Visit:** Dispense at least a 30-day and up to a 90-day supply of new tablets at site discretion (in addition to any returns the mother may have in her possession). Sites choosing to dispense a 30-day supply should plan interim “pharmacy only” visits to dispense more supplies between protocol-specified visits.
- **Postpartum Week 14, 26, and 38 Visits:** Dispense up to 90-day supply of new tablets at site discretion (in addition to any returns the mother may have in her possession). Sites choosing to dispense a 30-day supply should plan interim “pharmacy only” visits to dispense more supplies between protocol-specified visits.
- **Postpartum Week 50 Visit:** No study drug is permitted to be dispensed. Collect all remaining supplies from the mother at this visit.

## 9.3 Additional Considerations for Concomitant Medications

For this study, the term concomitant medications refers to medications other than the study drugs that comprise the maternal ART regimens listed in protocol Section 5.1. Protocol Section 5.8 provides further information related to concomitant medications.



Per protocol Section 5.8.1, *mothers in Arms 1 and 2 (i.e., the DTG-containing arms) who require cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications will be counseled to take these medications at least six hours before or at least two hours after taking DTG. Alternatively, DTG and supplements containing calcium or iron can be taken together with food.*

Many mothers in the study will take prenatal multivitamins that contain iron or calcium; many will also take antacids. Study site staff should proactively query mothers about use of these types of concomitant medications listed above and advise mothers on how these medications should be taken in relation to DTG. A few options are as follows:

- Example 1: Mothers may take the concomitant medication with DTG (and other ARVs) with food.
- Example 2: Mothers may take DTG (and other ARVs) then wait at least two hours to take the concomitant medication.
- Example 3: Mothers may take the concomitant medication then wait at least six hours to take DTG (and other ARVs).

#### 9.4 FAQs Related to Study Drugs and Concomitant Medications

##### 9-A We understand the EFV-containing study drug regimen should preferably be taken at bedtime. Is similar advice available for the DTG-containing regimens?

The DTG-containing regimens may be taken at any time that works well for each mother. Because DTG may be associated with insomnia, consideration may be given to suggesting that DTG-containing regimens be taken in the morning. For any mother who experiences insomnia, morning dosing should be recommended.

##### 9-B What instructions should be provided to mothers if they miss a dose of ARVs?

In general, if a mother realizes that she missed a dose within 12 hours of when she usually takes her ARVs, she should take the missed dose. If more than 12 hours have elapsed, she should wait and take the next scheduled dose at the usual time. Double doses should not be taken after a missed dose.

When providing this guidance to participants, site staff should take into consideration when a mother usually takes her ARVs (e.g., morning, afternoon, evening, bedtime) and tailor the instructions accordingly. Instructions should also include relevant agent-specific guidance for each ARV the mother is taking (e.g., EFV should be taken on an empty stomach).

##### 9-C What instructions should be provided to mothers if they vomit soon after taking study drug?

If a mother vomits within 15 minutes after taking her ARVs, she should take a replacement dose. If a mother vomits more than 15 minutes after taking her ARVs, she should not take a replacement dose unless she is able to identify one or more tablets in the vomitus.

**9-D If mothers cannot tolerate the ARVs they are randomly assigned to receive, can they be given other ARVs that are part of the other study drug regimens? Under LoA #1, we would also ask this same question for mothers who change regimens because they are not willing or able to use effective contraception postpartum.**

Refer to protocol Sections 5.4, 8.1, and 8.2 for further information on this topic.

Study-supplied ARVs are expected to be provided to mothers in Arms 1, 2, and 3 consistent with their random assignments. However, maternal ARV regimens may be changed as needed in response to toxicity or inability to tolerate the assigned regimen. Regimens may also be changed in cases of confirmed virologic failure and when treatment with a concomitant precautionary or prohibited medication makes a change of ARV regimen necessary. As noted in your question, regimens may also be changed in relation to contraceptive choice, as specified in LoA #1.

When a regimen change is necessary for any reason, all available study drugs, as well as ARVs available from non-study sources, may be used when constructing new regimens for mothers in any of the arms. All regimen changes involving DTG, EFV, TAF, or TDF should be made in consultation with the CMC.

As a reminder, all regimen changes involving DTG or EFV require conduct of a maternal Post ARV Switch Visit approximately four weeks after the regimen change.

**9-E We expect that some but not all mothers will take their first dose at the study clinic on the day of enrollment. For mothers who do not take their first dose of study drug at the clinic, are we required to document the date and time of first dose? If so, when should this be done?**

Enrolled mothers are generally expected to take their first dose of study drug on the day of enrollment. If for some reason this is not possible, the first dose should be taken on the day after enrollment. The actual date of the first dose should be recorded; it is not necessary to record the time of the first dose.

Refer to protocol Sections 5.2 and 8.7 for considerations related to the timing of maternal ARV dosing. On the day of enrollment, the protocol team encourages first dosing at the study site clinic. However, this is not required. For any mother who does not take her first dose at the clinic, the team strongly recommends that study staff proactively contact the mother to confirm that her first dose was taken (e.g., by telephone or home visit), ideally on the day after enrollment. In addition to confirming the date of first dose, per protocol Section 6.3, “Between scheduled visits, particularly in the first month of study participation, study site staff are encouraged to contact mothers to address any issues or questions about their study participation, clarify instructions for use of study drugs, and/or provide adherence counseling as needed.” All study sites should establish SOPs describing how they will do this.

The date of first dose of study drug will be entered into the Study Treatment Initiation eCRF (ADM10009), which is first required at the study Entry Visit. If the first dose is taken on the day of enrollment (either during the Entry Visit at the study site clinic or later that same day), this should be indicated on the ADM10009 eCRF entered for the Entry Visit. If the first dose is not taken on the day of enrollment, this should be indicated on the ADM10009 eCRF entered for the Entry Visit and another copy of the ADM10009 eCRF will need to be entered at the Antepartum Week 4 Visit. In this scenario, site staff must contact the Protocol Data Managers to request that a copy of the ADM10009 eCRF be added the Antepartum Week 4 Visit folder in Rave.

**9-F At our site, it is likely that study mothers who deliver in a hospital setting will receive a “loading dose” of zidovudine (ZDV) during labor and delivery. This would be in addition to the ART regimen that mothers will otherwise be taking for the study. Are there any study-related issues or concerns related to this?**

Thank you for informing the team about this. There are no study-related concerns related to this; however, it will be important to source document the ZDV dosing and enter this dosing into the Concomitant Medications Log eCRF (CMW10001).

**9-G Our site is a DXA site, and we generally expect mothers to undergo their DXA scans on a day after they complete other Week 50 study procedures (within the Week 50 visit window). In this case, when should a mother’s remaining supplies of study drug be collected?**

It is generally expected that mothers will continue taking study drug through completion of all Week 50 study procedures. Therefore, in the scenario that you describe, we would expect the mother’s study drug supplies to be collected on the day when she undergoes her DXA scan.

**9-H We have taken note of the advice in protocol Section 5.8.1 related to initiation of cotrimoxazole (CTX) or isoniazid (INH) prophylaxis preferably at least two weeks after initiation of study drug. Please advise on how we should manage potential participants who have already initiated CTX or INH at their screening or enrolment visits. Would these mothers be eligible for the study? If they are eligible, should be stop taking CTX or INH prophylaxis when they enroll?**

Any mothers who have already started CTX or INH prophylaxis per the local standard of care should stay on these medications. This would have no impact on their eligibility for the study. If you have any specific questions or concerns about this for any given participant, please contact the CMC.

**9-I In our setting, women are often started on acyclovir prophylaxis in the second trimester of pregnancy; however, acyclovir is listed as a precautionary medication with TAF, TDF, and FTC. How should we manage these participants?**

Acyclovir is considered precautionary with use of TAF, TDF, and FTC because of the potential to reduce renal function or compete for active tubular secretion. However, acyclovir is commonly prescribed for persons with HIV who are taking TAF, TDF, and FTC. There are no *a priori* concerns with use of acyclovir in this study and no additional monitoring or management is required for mothers who may receive acyclovir. In the event that a concern arises for any mother at your site, please contact the CMC.

**9-J The clinicians at our site have noted that NSAIDs are considered precautionary with TAF; specifically, high-dose or multiple NSAIDs should be used with caution with TAF. We would like to request some further guidance related to this. For example, what is considered high dose, and how should we manage mothers who take NSAIDs?**

The IMPAACT 2010 CMC has provided the information shown below regarding use of NSAIDs during pregnancy and postpartum:

NSAIDs can be used in pregnancy, but they have potential risks that must be balanced with potential benefits. If NSAIDs are clinically indicated for a pregnant woman, the lowest effective dose should be used for the shortest possible duration during pregnancy. There are also obstetric indications for NSAIDs, such as indomethacin used to stop uterine contractions in preterm labor, which can minimize some adverse pregnancy outcomes.

NSAIDs have been associated with increased risk of miscarriage and malformations if used early in pregnancy. If used later, particularly after 30 weeks gestation, they can cause premature closure of ductus arteriosus in the fetus and low amniotic fluid volume, as they cross the placenta. The specific effects of each drug would depend on the type of drug, dose, and duration, as well as gestational age.

After delivery, there is no significant concern for women taking normal doses of NSAIDs or taking NSAIDs for a short period of time. For women taking NSAIDs at high doses or for a longer period of time, there is no significant concern as long as the woman has normal renal function. You can consider “high dose” to be doses above the usual prescribed dose.

Consultation with the CMC is recommended with respect to NSAIDs, as follows:

- If a pregnant woman being screened for the study is taking a high-dose or long-term daily NSAID, her renal function should be checked (creatinine and CrCl are tested as part of study screening) and the CMC should be consulted on eligibility.
- If it is determined that an enrolled pregnant woman may need an NSAID, and that the benefit may outweigh the risk, the CMC should be consulted in this case as well.
- Lastly, if an enrolled mother starts taking a high-dose or long-term daily NSAID, the CMC should be consulted on management going forward in the study.

## 10.0 COUNSELING CONSIDERATIONS

This section provides guidance on the following types of counseling to be provided in IMPAACT 2010:

- HIV-related counseling
- Infant feeding counseling
- Contraception counseling
- Mental health counseling
- Study drug adherence counseling

### 10.1 Counseling Overview

All counseling provided in this study should be provided per site standard operating procedures (SOPs), which should reflect all national, international, and local policies and guidelines that are applicable at each site. Site SOPs should be reviewed and updated at least once annually and upon issuance of any updated policies and guidelines. SOPs should reflect the expectation that most mothers enrolled in this study will be newly diagnosed with HIV infection and will be starting a new antiretroviral study drug regimen upon entry into the study, while concurrently starting to cope with their new diagnosis and all its implications.

All study staff who provide counseling should be trained to do so in accordance with local standards of care and site training policies. Site supervisory staff are responsible for ensuring the quality of counseling provided through on-site monitoring, mentoring, and refresher training throughout the course of the study.

Counseling provided in this study may identify needs that are beyond the scope of the study to address. When such needs are identified, participants should be referred to non-study service providers and other organizations that may be able to assist them. Each site should maintain current lists of referral organizations and make these lists available to all counselors for use during all counseling sessions. At each counseling session after a referral is made, the counselor should actively follow-up on the referral to determine whether the participant sought the services to which he or she was referred, determine the outcome of the referral, and determine whether additional referrals are needed. Additional counseling may also be needed to help ensure that participants access services that may be beneficial to them.

All counseling must be documented in participant study records. Documentation should include the content of each counseling session, participant responses to the counseling provided, any concerns raised by the participant, action planned to be taken by the participant prior to the next counseling session, action to be taken by the counselor (or other study staff) prior to the next session, and issues to be reviewed or addressed at the next session. Specific to referrals, all follow-up actions, outcomes, counseling, and plans for next steps should also be documented. Study sites may choose to use checklists to document counseling sessions — particularly to document the content of each session — but it is expected that narrative notes will also be required to fully document each session. Careful attention should be paid to clearly identifying counseling issues to be addressed at the next session, given that different counselors may provide counseling at different visits.

## 10.2 HIV-Related Counseling

All sites will provide HIV-related counseling to mothers throughout their participation in the study. This counseling will include:

- ***Counseling in relation to maternal HIV testing:*** Most mothers enrolled in this study will undergo HIV testing as a study procedure, to confirm their eligibility for study participation. HIV testing must be performed in the context of pre-test and post-test counseling. Pre-test and post-test counseling should be provided per site SOPs in a client-centered manner, i.e., in a manner that is responsive to the information and counseling needs of the mother at the time of the session.
- ***Counseling in relation to infant HIV testing:*** All infants in this study will undergo HIV testing as a study procedure. At each testing time point, pre-test counseling should be provided to the infant's mother and test results should be provided to the mother in the context of post-test counseling. Pre-test and post-test counseling should be provided per site SOPs in a client-centered manner. If infants test positive for HIV infection, mothers may require additional post-test counseling to support their understanding and coping with the test results. All sites should offer additional counseling sessions in response to such needs.
- ***Counseling in relation to risk reduction:*** For this study, the term risk reduction counseling refers to counseling provided to support mothers in reducing their risk of re-infection and their risk of transmitting HIV to others (e.g., to sexual partners, to their infants). Risk reduction counseling should be provided as part of the pre-test and post-testing counseling described above and at any time in response to client-centered needs, per site SOPs.

Condoms should be provided throughout participation in the study and risk reduction counseling should include information, education, and skills building on condom use and condom negotiation strategies as needed for each mother. Counseling should also include HIV/AIDS education, discussion of disclosure issues and emotional support, discussion of healthy living strategies, discussion of stressors and potential strategies to address these, and provision of referrals, as applicable to each mother. Counseling for all mothers should include information on suppression of HIV viral load as an effective strategy to minimize the risk of transmission to others.

Mothers should also be counseled on the benefits of HIV counseling and testing for couples and study sites should offer counseling and testing for partners whenever possible.

## 10.3 Infant Feeding Counseling

All sites will provide infant feeding counseling to all mothers throughout their participation in the study. Consistent with international guidelines, infant feeding counseling should:

- Provide mothers with information about the risks and benefits of various infant feeding options
- Guide mothers in choosing the infant feeding option that is most likely to be suitable for their situation
- Support mothers in implementing the method they choose by helping them carry it out safely and effectively

This study will be conducted in a variety of settings worldwide. In some settings, country-specific infant feeding guidelines encourage breastfeeding among HIV-infected mothers; in others, country-specific guidelines encourage formula feeding. All sites are expected to follow their country-specific guidelines and any other applicable policies and guidelines. Infant feeding counseling should be provided per site SOPs and in a client-centered manner, responding to needs for information, guidance, and support that may change over time. Counseling should also be guided by information available from infant clinical assessments, which will monitor growth and weight gain over time.

## 10.4 Contraception Counseling and Provision

Refer to protocol Section 8.6.1. All sites will provide contraception counseling to mothers throughout their participation in the study. Counseling should be provided per site SOPs in a client-centered manner and should reflect study-specific requirements, local standard guidelines, locally available contraceptive methods, and site-specific plans for provision of contraceptive methods to study participants. When applicable, mothers should be offered the option of having their partners attend counseling sessions with them. Study sites should ideally integrate provision of contraceptive methods with other services offered to study participants and should provide referrals to non-study sources of methods that cannot be provided at the study site.

Contraceptive methods considered effective for this study are listed in LoA #1, inclusion criterion 4.1.8. LARCs (specifically, IUD/IUS or subdermal contraceptive implants) and injectable hormonal methods are strongly recommended due to their lower failure rates with typical use; mothers should be encouraged to use one of these methods. Sites are encouraged to use a tiered approach to counseling, beginning with information on methods that are most effective. The following references provide additional guidance on tiered counseling approaches:

- ***Typical use and perfect use effectiveness of contraceptive methods: Seven approaches to decrease unintended pregnancy (Contraceptive Technology)***  
<http://www.contraceptivetechnology.org/wp-content/uploads/2014/09/LB-13-Handout-Unintended-Pregnancies-7-Approaches-9-4-14.pdf>
- ***Decision-making tool for family planning clients and providers: A resource for high-quality counseling (WHO)***  
[http://www.who.int/reproductivehealth/publications/family\\_planning/9241593229index/en/](http://www.who.int/reproductivehealth/publications/family_planning/9241593229index/en/)
- ***Comparing effectiveness of family planning methods in Family Planning: A Handbook***  
<https://www.fphandbook.org/comparing-effectiveness-family-planning-methods>
- ***Effectiveness of family planning methods (CDC)***  
[https://www.cdc.gov/reproductivehealth/contraception/unintendedpregnancy/pdf/Contraceptive\\_methods\\_508.pdf](https://www.cdc.gov/reproductivehealth/contraception/unintendedpregnancy/pdf/Contraceptive_methods_508.pdf)

Additional reference information that sites may incorporate into their SOPs and counseling messages is available in the following:

- ***Technical Issue Brief: Drug interactions between hormonal contraceptive methods and anti-retroviral medications use to treat HIV (USAID)***  
[https://www.usaid.gov/sites/default/files/documents/1864/HC\\_ART-Brief.pdf](https://www.usaid.gov/sites/default/files/documents/1864/HC_ART-Brief.pdf)
- ***2016 WHO medical eligibility criteria for contraceptive use: Quick reference chart for Category 3 and 4 (WHO, USAID, FHI 360)***  
<https://www.fhi360.org/sites/default/files/media/documents/resource-chart-medical-eligibility-contraceptives-english.pdf>

Study-specific guidance on contraception options within the first 27 days after delivery is provided in Figure 10-1.

Key study-specific counseling messages are outlined in Figure 10-2; further visit specific guidance is outlined in Figure 10-3. A review of available methods should be provided — preferably using the tiered approach — including information on how each method is taken or administered, mechanisms of action, level of effectiveness, and potential advantages and disadvantages. Counseling should reflect the ARVs that mothers are currently taking and the potential interactions between these ARVs and available contraceptive methods. Counseling should guide and support each mother in making the best contraceptive method choice for her and should provide information, education, and skills-building to optimize adherence to the chosen method.

It is acknowledged that fertility intentions and contraceptive needs may change over time; contraceptive counseling provided over time should be responsive to any such changes. Some mothers may decline or stop use of effective contraception; this is acceptable. Some mothers may also wish to change contraceptive method over time; this is also acceptable. See also FAQ LoA-11 through LoA-17. Mothers should be supported in open and honest reporting of fertility intentions and adherence to contraceptive use.

**Figure 10-1**  
**Contraception Options for Use Within the First 27 Days After Delivery in IMPAACT 2010**

Contraceptive Method	Time of Initiation
<b>All women (breastfeeding and non-breastfeeding)</b>	
Female surgical sterilization (i.e., hysterectomy, bilateral oophorectomy, tubal ligation, or salpingectomy)	Within 72 hours after delivery
Contraceptive intrauterine device or system (IUD/IUS)	Within 48 hours after delivery
Subdermal contraceptive implant	Any time after delivery
Progestogen-only injections (e.g., DMPA)	Any time after delivery*
Progestogen-only oral contraceptive pills	Any time after delivery
<b>Non-breastfeeding women only</b>	
Combined estrogen and progestogen methods (including percutaneous contraceptive patches, contraceptive vaginal rings, or oral contraceptive pills)	From third week after delivery <sup>†</sup> (i.e., can begin after Day 21)
<p>Note: Male or female condom use is recommended with all contraceptive methods for dual protection against pregnancy and to avoid transmission of HIV and other sexually transmitted infections.</p> <p>*Unless in-country guidelines state otherwise.</p> <p><sup>†</sup>Only if none of the following risk factors for venous thromboembolism (VTE): age ≥35 years, previous VTE, thrombophilia, immobility, transfusion at delivery, peripartum cardiomyopathy, BMI ≥30 kg/m<sup>2</sup>, postpartum hemorrhage, post-cesarean delivery, preeclampsia, or smoking.</p> <p>References:</p> <ul style="list-style-type: none"> <li>– WHO Method Eligibility Criteria 2015 <a href="http://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/">http://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/</a></li> <li>– CDC Medical Eligibility Criteria 2016 <a href="https://www.cdc.gov/mmwr/volumes/65/rr/rr6503a1.htm?s_cid=rr6503a1_w">https://www.cdc.gov/mmwr/volumes/65/rr/rr6503a1.htm?s_cid=rr6503a1_w</a></li> </ul>	



**Figure 10-2**  
**Contraceptive Counseling Messages for Mothers in IMPAACT 2010**

All contraceptive counseling sessions should provide information, education, skills building, and referrals in response to current needs. At each session, issues requiring follow-up from the prior session should be reviewed and updated, and plans should be made for actions to be taken between the current session and the next session. Instructions and counseling for proper use and adherence to the current contraceptive method should be reviewed and reinforced at each session.

- ✓ Counsel on the benefits of child spacing for maternal and child health
- ✓ Emphasize the benefits of long-acting reversible methods compared to other methods — including higher effectiveness with typical use
- ✓ Recommend consistent use of male or female condoms with all contraceptive methods, for dual protection against pregnancy and transmission of HIV and other sexually transmitted infections. Emphasize the importance of condom use during the early postpartum period prior to initiation of effective contraception.
- ✓ Highlight the importance of avoiding pregnancy while on DTG (for mothers taking DTG postpartum). Explain, if applicable, that study-supplied DTG can only be provided to mothers who are willing and able to use effective contraception.
- ✓ Emphasize that contraceptive choices will have no impact on continued study participation
- ✓ Encourage open and honest reporting of fertility intentions and adherence to contraceptives
- ✓ Actively remind mothers to inform study staff if they:
  - Wish to become pregnant again
  - Suspect that they may be pregnant
  - Miss any doses of contraception
  - Wish to change contraceptive method

**Figure 10-3**  
**Visit-Specific Contraceptive Counseling Guidance for IMPAACT 2010**

As described in LoA #1, contraception counseling should be provided to all mothers at each study visit. Visit-specific guidance is as follows:

- ✓ **Screening and Entry Visits:** Assess future fertility intentions and willingness to use effective contraception following the current pregnancy.
- ✓ **Antepartum Week 4 Visit:** Provide contraception counseling and document plan for initiating effective contraception postpartum.
- ✓ **All Subsequent Antepartum Visits:** Provide contraception counseling and review and update (if applicable) plan for initiating effective contraception postpartum.
- ✓ **Delivery Visit:** Provide contraception counseling and finalize previously-discussed plans for initiation of effective contraception.
  - Mothers choosing contraceptive methods that are clinically appropriate to initiate as of the date of the Delivery Visit should initiate their chosen method at the visit (if not already initiated).
  - Other mothers may return for an additional visit for this purpose (*refer to LoA #1 item 20 for more information on conducting a split Delivery Visit in this context*).
- ✓ **All Postpartum Visits:** Provide contraception counseling at each visit; actively facilitate access to contraceptive services and, to the extent possible, provide contraceptive services on-site.

## 10.5 Mental Health Counseling

Refer to protocol Section 8.7. Mothers in this study may experience nervous system symptoms associated with EFV and, less commonly, with DTG. Psychiatric adverse events, including severe depression and suicidal ideation or attempt, have also been observed with use of EFV, and rarely with DTG.

Medical history information will be collected at all maternal study visits and standardized questionnaires related to depression, anxiety, and sleep disturbances will be administered at selected timepoints during follow-up; refer to Sections 8.6, 8.7, and 8.8 of this manual for more information on questionnaire administration.

Through these procedures, potential mental health issues or problems may be identified. Designated study staff should discuss any such issues or problems with the mother to determine whether any grade 1 or higher adverse events have occurred and whether any additional support, evaluation, and/or treatment may be of benefit to the mother. Study staff are not expected to provide such mental health services. However, all sites must establish SOPs for referral to non-study sources of such services. **The availability of such services should be routinely communicated to all mothers** and any mothers who express interest in such services at any time should be referred accordingly, regardless of questionnaire responses and/or the assessed severity grade of any adverse events. That is, all mothers should be informed of available services and any mother who feels that she wants or needs additional services should be referred accordingly.

While referral is generally expected to be at the choice of the mother, special attention must be paid to any reports of suicidal ideation (with or without a plan) or attempt, including but not limited to such reports in response to item 10 of the EPDS. **Any mother who reports suicidal ideation or attempt must be referred to appropriate mental health services.** Mothers with other potential mental health issues of concern, even in the absence of suicidality, may also be referred at the discretion of the investigator or designee. The nature and timing of each referral should reflect the type and severity of the symptoms reported. For example, a mother with suicidal ideation and a plan should be referred immediately, potentially accompanied to a mental health provider, rather than being sent home pending further follow-up.

## 10.6 Study Drug Adherence Counseling

Refer to protocol Section 5.7. All sites will provide study drug adherence counseling to all mothers throughout their participation in the study.

The purpose of adherence counseling is to provide information, skills building, and other guidance to support mothers in taking ARVs as correctly and consistently as possible. While it is essential that mothers be provided information on correct use of each ARV, once this knowledge is established, the emphasis of adherence counseling should be on supporting the mother in consistent use over time.

Adherence counseling should be provided in a client-centered manner per site SOPs. Site SOPs should designate roles and responsibilities for adherence assessment, counseling, and support and specify how clinic and pharmacy staff will share information and coordinate efforts while fulfilling their respective roles and responsibilities. **For this study, site SOPs must specify a two-tiered approach to adherence counseling.** The first tier should describe routine adherence counseling for mothers who are generally adherent and for whom significant barriers to adherence are not identified. The second tier should describe enhanced adherence counseling for mothers for whom significant barriers to adherence are identified (including mothers who do not achieve or sustain a suppressed HIV viral load).

Adherence counseling should acknowledge that consistent use of ARVs is challenging and should encourage mothers to openly discuss any challenges they may face, so that study staff can assist with identifying strategies to address the challenges. Counseling should also acknowledge that adherence challenges may change over time; therefore, adherence strategies may also need to change over time. The role of the counselor is to support the mother in identifying strategies that are most likely to work for her.

Additional tips and guidance for providing adherence counseling are as follows:

- In preparation for each counseling session, review study records to:
  - Identify how long the mother has been taking ARVs; whether she has experienced ARV side effects; whether she has achieved and/or sustained a suppressed HIV viral load; and whether adherence challenges have been encountered to date.
  - Obtain current information on other key issues such as the HIV status of the mother's infant
  - Review the adherence strategies that have been identified for the mother to date and which of these have been perceived as successful or unsuccessful by the mother; pay particular attention to adherence strategies identified at the last counseling session.
- Prepare any materials that may be needed for the session.

- Greet the mother by name, establish rapport, and foster open dialogue. Reinforce confidentiality and explain that the purpose of the session is solely to assist the mother with taking her ARVs.
- Understand that the mother is likely to be concerned about HIV transmission to her infant. She may also be concerned about her own health, in the short and/or long terms. Adopt a neutral and non-judgmental but supportive approach to assist the mother in coping with these concerns in relation to adherence to her ARVs.
- Invite the mother to ask any questions and express any concerns she may have.
- As needed, address any knowledge gaps or misinformation with regard to use of ARVs. Use information sheets and/or other visual aids to help ensure the mother's understanding of instructions for correct use of each ARV, paying particular attention to these issues as mothers enter the study and when ARV regimen changes occur.
- As needed, provide skills building support to the mother (e.g., on proper storage of ARVs; on disclosure of HIV status and/or study participation to others).
- Use open-ended questions and actively listen to the mother's responses to assess her experience with adherence since her last visit.

*Note:* Adherence questionnaire data collected as described in Section 8 of this manual may **not** be used as a basis for adherence counseling in this study. Rather, client-centered dialog should guide all counseling.

- Incorporate discussion of HIV viral load test results and trends in these results over time. If results and trends are not as expected, ask the mother for her thoughts on why this may be the case and build from the mother's perceptions to guide additional counseling.
- Provide positive reinforcement for adherence successes. Ask the mother to share more information on successful strategies so that her approaches can be shared with other study participants. Continue successful strategies as part of the mother's ongoing adherence plan.
- Review the adherence strategies discussed at the previous session and probe as needed to identify ongoing or new barriers to adherence. With continued dialog, assess whether the reminder and adherence strategies discussed at the previous session were perceived by the mother as useful/successful. As needed, assist the mother with identifying new strategies to try to address new or ongoing barriers.
- At each session, clearly articulate the adherence plans and strategies identified by the mother for the time period between the current session and the next session. All plans and strategies should be practical and feasible for the mother. For mothers with significant adherence barriers, plans and strategies may need to be incremental. For mothers whose adherence barriers change over time, plans and strategies may also need to change over time. All plans and strategies should be documented in study records with written copies given to the mother, if desired.
- Thank the mother for her and her infant's participation in the study. Acknowledge the contributions they are making toward finding new treatments for mothers with HIV and improving the health of mothers and infants worldwide.

## 11.0 PARTICIPANT MANAGEMENT CONSIDERATIONS

Protocol Section 8 describes management of maternal and infant adverse events; monitoring and management of maternal HIV viral load; and management of other selected conditions relevant to the study population. FAQs related to adverse event grading and reporting, which are relevant to protocol Sections 8.1 and 8.2, as well as protocol Section 7.2, are provided below. Other FAQs and operational guidance related to participant management will be added to this section as needs for such guidance are identified.

**11-A Section 8.3 of the protocol states that the CMC should be consulted regarding management of mothers who interrupt ART for a period of 14 or more days. Does this refer to 14 or more consecutive days?**

Yes.

**11-B We understand that this study involves limited adverse event reporting. If we enter an event into an eCRF that does not meet protocol criteria for reporting, will the Rave system alert us to this?**

No. The Rave system is not programmed to proactively identify adverse events that do not meet protocol-specified reporting criteria. Therefore, the system will not alert you if any such events are entered.

**11-C The instruction in protocol Section 7.3.3 regarding maternal weight loss in this study appears to differ from instructions provided in other IMPAACT studies. Can you confirm that postpartum weight loss should not be graded in this study?**

Yes. As specified in protocol Section 7.3.3, and consistent with Corrected Version 2.1 of the DAIDS Grading Tables used for this study, postpartum weight loss is not expected to be graded in this study. Nonetheless, maternal weight should be evaluated at all scheduled study visits. In the event that a mother experiences postpartum weight loss that is assessed by the study clinician as greater than expected or intended, please consult the CMC for further guidance.

**11-D We have noted that the Pregnancy, Puerperium, and Perinatal section of the DAIDS Adverse Event Grading Table includes severity grading for spontaneous abortion or miscarriage, fetal death or still birth, and preterm birth. The Grading Table indicates that these conditions should be reported under the mother's PID. With respect to reporting of "preterm birth," does this mean that we should not report "preterm birth" or "prematurity" for infants?**

Yes, that is correct. Preterm birth should be source documented as a maternal adverse event and entered into the Adverse Event Log eCRF if the condition meets criteria in protocol Section 7.2.1 (for the mother). The same event should not also be recorded for the infant.

**11-E We understand that small for gestational age (SGA) is a safety outcome for this study. Do we need to assess SGA based on WHO norms at the site and enter this assessment into eCRFs? If an infant is assessed as SGA, should this be entered into the Adverse Event Log eCRF?**

For this study, the assessment for SGA will be performed by the protocol statisticians, based on each infant's gestational age and weight at birth. As such, study sites are not expected or required to assess for SGA or to enter assessments for SGA into eCRFs (including Adverse Event Log eCRFs).

**11-F We have noted that the DAIDS severity grading for spontaneous abortion uses the term “chemical pregnancy.” What does this mean?**

DAIDS defines this term as follows: A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.

**11-G In Section 7.3.2, the protocol states that pregnancy complications that result in medically indicated and/or elective termination of the pregnancy should be reported as expedited adverse events. We understand that this would include early terminations of a pregnancy in which the fetus is not expected to survive. Would this also include situations in which a decision is made to induce labor early or perform a cesarean section?**

In this context, “termination” was intended to refer to ending a pregnancy with the expectation that the fetus would not survive (i.e., abortion). This is in contrast to early induction of labor or performance of a cesarean section with the goal of saving the fetus. It should be noted, however, that complications leading to early induction of labor or performance of a cesarean section to save a fetus may require EAE reporting, depending on the nature of the complication. Please contact the CMC with any questions about EAE reporting for any mother-infant pair.

## 12.0 EXPEDITED ADVERSE EVENT REPORTING REQUIREMENTS

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

- Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0)
- DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, dated July 2017
- Study drug package inserts:
  - Dolutegravir (Tivicay)
  - Emtricitabine/tenofovir disoproxil fumarate (Truvada)
  - Emtricitabine/tenofovir alafenamide (Descovy)
  - Efavirenz (Sustiva)
  - Efavirenz/emtricitabine/tenofovir disoproxil fumarate (TEEVIR)
- DAERS Site User Instructional Guide for EAE Reporting
- DAERS Reference Guide for Site Reporters and Study Physicians
- DAIDS safety training resources

The DAERS and DAIDS resources listed above are available at:

<https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-experience-reporting-system>  
<https://rsc.niaid.nih.gov/clinical-research-sites/safety-training-resources>

LoA #1 harmonized EAE reporting requirements for all study participants, regardless of random assignment or maternal ART regimen. To illustrate the requirements, several reporting examples are provided below. When reviewing these examples, please note that even when EAE reporting is not required, all maternal and infant adverse events must be source documented and selected adverse events must be entered into eCRFs, per protocol Section 7.2.

Sample Case Description	Has a reportable EAE occurred?
1. A pregnant woman enrolled/randomized to Arm 1 at 18 weeks gestation is hospitalized at 20 weeks gestation with a febrile illness.	<b>Yes.</b> This event is serious because it resulted in hospitalization and, for mothers in all study treatment arms, all SAEs must be reported as EAEs.
2. A pregnant woman enrolled/randomized to Arm 2 at 18 weeks gestation is hospitalized at 20 weeks gestation with a febrile illness.	<b>Yes.</b> This event is serious because it resulted in hospitalization and, for mothers in in all study treatment arms, all SAEs must be reported as EAEs.
3. A pregnant woman enrolled/randomized to Arm 3 at 18 weeks gestation is hospitalized at 20 weeks gestation with a febrile illness.	<b>Yes.</b> This event is serious because it resulted in hospitalization and, for mothers in in all study treatment arms, all SAEs must be reported as EAEs.
4. A pregnant woman enrolled at 22 weeks gestation experiences a fetal death at 28 weeks gestation.	<b>Yes.</b> For mothers in all study treatment arms, fetal deaths must be reported as EAEs.

Sample Case Description	Has a reportable EAE occurred?
5. An enrolled pregnant woman reports to the clinic for her antepartum Week 4 visit complaining of severe fatigue, nausea, vomiting, and abdominal pain. Lab testing provides grade 4 ALT and AST results	<b>Maybe.</b> This case is intended to highlight the protocol requirement to report hepatic toxicities that result in discontinuation of DTG or EFV as EAEs in all study treatment arms. In this case, EAE reportability will depend on whether the event is assessed as meeting the definition of serious <u>and</u> on how the woman's symptoms are managed, including whether DTG or EFV is discontinued.
6. An enrolled pregnant woman begins labor at about 5:00 PM and delivers a healthy full-term infant at the local hospital at about 10:00 PM. Mother and infant remain in the hospital overnight and are discharged home the next day.	<b>No.</b> In this case, mother and infant have experienced a normal delivery, with no indication in the case description that an adverse event has occurred. Although the mother and infant remained in the hospital overnight, reportable events have occurred and no EAE reporting is required. <i>Note:</i> See Section 3.1 of the DAIDS EAE Reporting Manual for further guidance on hospitalization in relation to the definition of SAE.
7. An enrolled pregnant woman begins labor at about 5:00 PM. She experiences greater than normal blood loss during delivery, requiring transfusion. The infant is born alive and healthy but the mother remains anemic post-delivery and is kept in the hospital for further observation and care. She is then discharged home two days after delivery.	<b>Yes.</b> This event is serious because it resulted in prolongation of hospitalization and, for mothers in all study treatment arms, all SAEs must be reported as EAEs.
8. An enrolled pregnant woman delivers a full-term infant. Soon after delivery, the infant is found to have a fever and sepsis is suspected; the infant is then transferred to the neonatal special care unit of the hospital where he was delivered.	<b>Yes.</b> This event is serious because it resulted in prolongation of hospitalization and, for infants in all study treatment arms, all SAEs occurring through Week 14 must be reported as EAEs.
9. An enrolled pregnant woman delivers a full-term infant who is found to have an additional toe on his left foot.	<b>No.</b> As clarified in Section 3.1 of the DAIDS EAE Reporting Manual, clinically insignificant isolated physical findings at birth, including those regarded as normal variants, such as polydactyly or Mongolian spots, do not meet the definition of serious.
10. An infant is found to be clinically well at the Delivery Visit. However, laboratory results from this visit include a grade 4 absolute neutrophil count.	<b>No.</b> As described, this event does not meet the definition of serious. <i>Note:</i> The DAIDS Table for Grading Adult and Pediatric Adverse Events identifies grade 4 adverse events as potentially life-threatening. As such, it is not expected that all grade 4 events will be assessed as serious. Rather, each grade 4 event should be assessed for seriousness according to whether the event is immediately life-threatening (i.e., placing the participant at immediate risk of death). In this case, there is no indication in the case description that the event placed the infant at immediate risk of death.



Sample Case Description	Has a reportable EAE occurred?
11. At postpartum Week 6, a mother discloses suicidal thoughts, including a plan of how she could end of her own life, to the study clinician.	<b>Maybe.</b> For mothers in all study treatment arms, EAE reportability would depend on whether the suicidal ideation is assessed as serious.
12. Between the Week 6 and Week 14 visits, an infant is hospitalized with a respiratory infection that is diagnosed as pneumonia. In the hospital, the diagnosis of pneumonia results in the infant being tested for HIV, and the test is positive for infection.	<b>Yes.</b> The pneumonia is serious because it resulted in hospitalization and, for infants in all study treatment arms, all SAEs occurring through Week 14 must be reported as EAEs. <i>Note:</i> The infant's HIV infection would not generally be expected to meet the definition of serious.
13. An infant presents for his Week 14 visit with signs and symptoms of severe gastroenteritis. The mother is reluctant to have the infant admitted to hospital because she has other children at home to care for. The infant is therefore treated at the clinic with antibiotic fluids and other medicines.	<b>Yes.</b> The event is serious because, although the infant was not hospitalized, the gastroenteritis is an important medical event that requires intervention to prevent a serious outcome. For infants in all study treatment arms, all SAEs occurring through Week 14 must be reported as EAEs.
14. A mother-infant pair miss their postpartum Week 26 visits. Locator efforts identify that both mother and infant have been hospitalized for treatment of injuries sustained in a motor vehicle accident.	<b>Yes</b> for the mother. The mother's injuries are serious because they resulted in hospitalization and, for mothers in all study treatment arms, all SAEs must be reported as EAEs. <b>Maybe</b> for the infant. The infant's injuries are serious because they resulted in hospitalization but, for infants in all study treatment arms, after Week 14, EAE reportability depends on the site's assessment of relationship to study drug and expectedness. If the injuries are assessed as related to study drug and unexpected in relation to the study drug package inserts, the injuries would meet the definition of SUSAR and would need to be reported as an EAE.
15. A mother is identified with a new pregnancy at Week 38 postpartum. About six weeks later, she reports to the clinic with vaginal bleeding, and pregnancy testing indicates she has experienced a spontaneous abortion.	<b>Yes.</b> For mothers in all study treatment arms, spontaneous abortions must be reported as EAEs.
16. A mother-infant pair miss their Week 50 postpartum visits. Locator efforts identify, through family report, that the mother fell ill and died while visiting relatives approximately 5 weeks ago.	<b>Yes.</b> Although the cause of death is not yet known, the condition resulted in death and therefore meets the definition of serious. For mothers in all study treatment arms, all SAE must be reported as EAEs.

## 13.0 LABORATORY CONSIDERATIONS

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

This remainder of this section provides detailed operational instructions for hair collection. FAQs and other operational guidance will be added to this section as needs for such guidance are identified.

### 13.1 Hair Collection

Hair should be collected from all mothers and infants at the Delivery Visit.

#### 13.1.1 Materials Required

- Small pair of scissors
- Alcohol wipes
- Aluminum/tin foil. Cut into squares approximately 5 cm x 5 cm and fold into quarters.
- Zipper bags
- Labels (2) with PID; visit; collection date and time; and collector's initials
- Desiccant pellets (optional)
- IMPAACT 2010 Pharmacokinetics Specimen Tracking Log (PKW10003)



As shown in the above picture, study sites should prepare the hair collection bags with all supplies needed for hair collection prior to a participant visit.

### 13.1.2 Collection Procedure

- a. Clean the blades of a pair of scissors with an alcohol pad and allow blades to completely dry prior to use.



- b. Unfold the piece of foil before cutting the hair.
- c. Lift up the top layer of hair from the occipital region of the scalp. Isolate a small thatch of hair (~100 strands) from underneath this top layer of hair (can use a hair clip to keep the top layer of hair away). **For infants:** Isolate a small thatch (~100 strands) from the back of infant's head.



- d. Cut the hair sample (~100 strands) off the patient's head as close to the scalp as possible, keeping fingers firmly on part farthest from scalp (distal end).



- e. For short hair, collect straight into foil; no need to label distal end (1 cm = 1 month growth)





- f. For braided hair, collect from short strands between braids.



- g. Place the cut thatch of hair inside the piece of foil with fingers over the distal end.



- h. Place a small label with the participant PID over the distal end of the hair thatch (the side furthest away from the scalp).



Label with  
PID; visit;  
collection date  
and time; and  
collector's  
initials



- i. Refold the foil over to completely enclose the hair. Place a Label with PID; visit; collection date and time; and collector's initials on the top of the foil. Place the folded piece of foil inside the plastic zipper bag. Place a desiccant in each bag (optional) and seal the bag.



- j. Complete/enter PKW10003.

### 13.1.3 Storage of Hair

Hair samples should be logged into the LDMS and the zipper bags should be labeled with LDMS-generated labels. Hair samples should be kept at room temperature and in a dark place at each site until a request is received to ship the samples for testing.

## 14.0 DATA MANAGEMENT CONSIDERATIONS

Refer to protocol Section 10 and the eCRF completion guide developed by the DMC for this study. eLearning modules and other operational guidance on use of the Medidata Rave system for this study are available on the DMC portal.

FAQs related to eCRF completion are provided below. Also provided below, at site request, are tables (14-1 and 14-2) that map the maternal and infant medical and medication history elements specified in protocol Tables 3 and 4 to the eCRFs into which these elements will be entered. A series of scenarios is also provided (following Tables 14-1 and 14-2) to illustrate key aspects of eCRF data entry for adverse events.

**14-A Based on protocol Table 3, we believe that HIV infection should be recorded on the Medical History Log eCRF for all mothers who are enrolled in the study. Is this correct?**

Yes.

**14-B The Obstetric History eCRF (OBW10000) captures maternal pre-pregnancy weight. What source should we use for this information?**

A documented pre-pregnancy weight (e.g., from non-study medical records) is preferred. If a documented weight is not available, then the mother's report should be used. If neither of these is available, then this item should be left blank.

**14-C We are not sure that we understand the instructions for entry of ARV use data into eCRFs. Could you please clarify on this?**

The four study drug formulations listed in protocol Section 5.1 — DTG, FTC/TAF, FTC/TDF, and EFV/FTC/TDF — should be entered into the Treatment Log eCRF (TXW10001). All other ARVs should be entered into the Concomitant Medications Log eCRF (CMW10001). Further details are as follows.

For mothers:

- All ARVs received during prior pregnancies and prior periods of breastfeeding should be entered into the Concomitant Medications Log.
- All ARVs received in the current pregnancy, prior to enrollment, should be entered into the Concomitant Medications Log.
- The four study drug formulations listed in protocol Section 5.1, i.e., DTG, FTC/TAF, FTC/TDF, and EFV/FTC/TDF, received after enrollment, should be entered into the Treatment Log.
- All other ARVs received after enrollment should be entered into the Concomitant Medications Log.

For infants:

- All ARVs received should be entered into the Concomitant Medications Log.



**14-D We have some questions about data entry for mothers who change their ARV regimens. For example, on which eCRFs should we enter data for (i) mothers who may switch from DTG+FTC/TAF to EFV+FTC/TAF and (ii) mothers who may switch from DTG+FTC/TDF to EFV/FTC/TDF?**

As noted in item 14-C above, the study drug formulations listed in protocol Section 5.1 should be entered into the Treatment Log eCRF (TXW10001) and all other ARVs should be entered into the Concomitant Medications Log eCRF (CMW10001).

For (i) mothers who switch from DTG+FTC/TAF to EFV+FTC/TAF:

- Discontinuation of DTG should be entered into the Treatment Log eCRF.
- Initiation of EFV (single agent tablet obtained from non-study sources) should be entered into the Concomitant Medications Log eCRF.

For (ii) mothers who switch from DTG+FTC/TDF to EFV/FTC/TDF:

- Discontinuation of DTG+FTC/TDF should be entered into the Treatment Log eCRF.
- Initiation of EFV/FTC/TDF should be entered into the Treatment Log eCRF.

**14-E We are not sure that we understand the protocol requirement to enter into eCRFs all concomitant medications “taken at onset of” adverse events that are specified to be entered into eCRFs per Section 7.2. Could you please explain this?**

The intent of this instruction is to require entry of all concomitant medications that a participant is taking at the time when an adverse event that meets criteria in protocol Section 7.2 occurs. For example:

Consider a mother who receives a five-day course of antibiotics to treat a grade 2 respiratory infection. The respiratory infection would generally not be expected to meet criteria in protocol Section 7.2 for entry into the Adverse Event Log eCRF. In this scenario, the antibiotics would need to be source documented, but would not need to be entered into the Concomitant Medication Log eCRF.

Now consider a different mother who receives a five-day course of an antibiotic to treat a grade 2 respiratory infection. The respiratory infection would again not be expected to meet criteria in protocol Section 7.2 for entry into the Adverse Event Log eCRF. Suppose, however, that the mother experiences a grade 2 rash starting on the third day of her antibiotic treatment. In this scenario, the rash would need to be entered into the Adverse Event Log eCRF. In addition, because the antibiotics were being taken when the rash occurred (i.e., at onset of the rash), the antibiotics would need to be entered into the Concomitant Medication Log eCRF.

**14-F We have a question about entering laboratory data into eCRFs. When we enter hematology and chemistry test results and severity grades, will Rave automatically check the severity grades in real time?**

Yes. When the laboratory eCRF is saved, a custom function will check the severity grade and an automatic query will be generated if there is a discrepancy between the laboratory value and the grade. Please note, however, that this function only checks grades based on the absolute values of laboratory test results. It does not check grades based on change from baseline. Should you encounter difficulty with entering correct severity grades or resolving queries related to severity grades, please contact the Protocol Data Managers.

**14-G We are confused by the instructions for completion of the LBW10009 eCRF. Can you clarify which laboratory test results are required to be entered into this eCRF?**

Per protocol Section 7.2, it is not expected that the results of all laboratory tests performed for this study will be entered into the laboratory eCRF (LBW10009). Only the following are required to be entered into laboratory eCRFs:

For mothers

- All creatinine and creatinine clearance results
- All glucose results
- All hematocrit results from the Screening and Delivery Visits
- All grade 1 or higher LFT results
- All grade 3 or higher hemoglobin, white blood cell count, absolute neutrophil count, and platelet count results
- All results that lead to a change of ART regimen (i.e., any hold, discontinuation, switch/replacement, dose or frequency modification)
- All results that are serious as defined in Version 2.0 of the DAIDS EAE Manual
- All results that are relevant to events that meet criteria for reporting as EAEs (see Section 7.3.2)

Also for mothers, all pregnancy test results are required to be entered into the Pregnancy Test eCRF (LBW10005).

For infants

- All creatinine results
- All glucose results
- All hematocrit results from the Delivery Visit
- All grade 2 or higher ALT results
- All grade 3 or higher hemoglobin, white blood cell count, absolute neutrophil count, and platelet count results
- All results that are serious as defined in Version 2.0 of the DAIDS EAE Manual

Any other test results (e.g., Grade 1 or Grade 2 hemoglobin) do not need not be entered into laboratory eCRFs.

**14-H The LBW10009 eCRF includes fields for laboratory reference ranges for creatinine clearance (CrCl) rates. Our site does not have reference ranges established. How should we handle this?**

On 19 March 2018, the Protocol Data Managers notified the Protocol Team and study sites that reference ranges are not required to be entered into the LBW10009 eCRF for CrCl rates. The computerized data checks for these reference ranges will be adjusted accordingly. In the meantime, please contact the Protocol Data Managers to close any queries that may arise. Reference ranges remain required for all other laboratory values entered into the LBW10009 eCRF.

**14-I After watching the infant surface exam training video, we have some questions about the number of decimal places to enter into eCRFs for infant measurements. Could you please confirm?**

- Weight: if measuring in grams, round to a whole number.
- Weight: if measuring in kilograms, round to two decimal places.
- Length: measuring in centimeters, round to one decimal place.
- Head circumference: measuring in centimeters, round to one decimal place.

**14-J We have noted that the protocol requires documentation of the outcomes of subsequent pregnancies. When the time comes to do this, will we need to calculate a form week associated with the pregnancy outcome?**

No. When the time comes to document subsequent pregnancy outcomes, the eCRFs completed for this purpose will be linked to the mother's Postpartum Week 50 visit. The date of pregnancy outcome will need to be recorded, but it will not be necessary to calculate a form week associated with this date.

**14-K We have noted that congenital anomalies that may occur among infants from subsequent pregnancies need to be entered into eCRFs. Do we need to perform physical examinations of these infants in order to complete the relevant eCRFs?**

No. The protocol does not specify examination of subsequent infants as a study procedure (subsequent infants are not study participants). Therefore, the general expectation is that available non-study medical records will be used. In the event that an anomaly is identified, we would ask that the study clinician obtain as much information as possible, which may include requesting additional information/documentation from the clinician who examined the infant at birth (or soon thereafter).

**14-L Our site is a DXA site, and we generally expect mothers to undergo their DXA scans on a day after they complete other Week 50 study procedures (within the Week 50 visit window). In this case, when should a mother's "off study" eCRFs be entered?**

It is generally expected that off study eCRFs will be entered after all Week 50 procedures have been completed. Therefore, in the scenario that you describe, we would expect the off study eCRFs to be entered after the mother has undergone her DXA scan.

**14-M The primary indication for concomitant medications needs to be entered into the IMPAACT 2010 Concomitant Medications Log (CMW10001). There are four options for this: prophylaxis, optimized background regimen, treatment, and contraceptive use. Is there general guidance for what type of medication would fall into each category? For example, one of our mothers had a cesarean section; which category would the medications listed below be included in?**

Site investigators should use their best judgement when categorizing the indication for concomitant medications; however, the team can provide guidance shown below.

For this study, it is generally not expected that “optimized background regimen” will be used, as full maternal antiretroviral regimens are provided as part of study treatment (this option generally refers background ART or TB regimens to which new or alternate therapies are added).

In addition, as described in FAQ LoA-6, it is not necessary to enter all medications received during the intrapartum period into eCRFs. These medications should only be entered into eCRFs if they meet other criteria for eCRF entry.

<b>Example Concomitant Medication</b>	<b>Potential Primary Indication</b>
Spinal anesthetics	Treatment
Other drugs, for example, phenylephrine used for blood pressure control during anesthetics	Treatment
Antibiotics given prophylactically during and after C-section	Prophylaxis
Antacid and anti-nausea medication given prophylactically prior to C-section	Prophylaxis
Anti-nausea medication given post C-section prevent nausea due to morphine	Prophylaxis
Oxytocin, which is given during labor and delivery for all deliveries	Prophylaxis, usually (to prevent postpartum hemorrhage); Treatment (e.g., to induce labor)
Anti-clotting medication given prophylactically after C-section (i.e., clexane)	Prophylaxis
Analgesia post C-section (e.g., morphine, Brufen)	Treatment
Laxative given post C-section to prevent constipation due to morphine	Prophylaxis
Pregnancy supplements	Prophylaxis, usually; Treatment (e.g., iron supplements to treat anemia)
Contraceptives	Contraceptive use

**14-N We expect that some mothers will have an IUD inserted or have a sterilization procedure performed while that are in the hospital, immediately postpartum. Do we understand correctly that we should enter IUDs and sterilization procedures (e.g., tubal ligation) into the con meds eCRF?**

Yes, that is correct.

**14-O We are having difficulty entering data for Delivery Visits in Rave. For example, we have a mother who completed her Antepartum Week 4, Week 8, and Week 12 visits, and then delivered two weeks later. We can see the Antepartum Week 16 visit folder in Rave, but we cannot access the Delivery Visit folder for the mother and the newborn baby. Could you explain what we should do?**

For the mother:

1. Navigate to the next available Antepartum Visit week folder (in this example, it would be the Antepartum Week 16 folder). In that folder, indicate that the visit occurred. This will make the SVW10001: IMPAACT 2010 Study Event Tracking – Maternal eCRF available in Rave.
2. Navigate to the SVW10001 eCRF in the Antepartum Week 16 visit folder. When completing the SVW10001: IMPAACT 2010 Study Event Tracking – Maternal eCRF, you will need to select NO for all required questions except item 16, “At this visit or since the last visit, has the mother delivered or had another outcome for the index pregnancy?” This question must be answered YES to roll out the Maternal Delivery visit folder. Respond NO to all other required questions; this is crucial to ensure that all data for the Delivery visit are reported in the delivery visit folder.
3. Then navigate back to the participant’s page (where all folders for the mother can be seen). The Maternal Delivery Visit folder should now be available.
4. Navigate to the Maternal Delivery visit folder and complete it accordingly.

*Note 1:* Make sure to use the same visit date as the Antepartum Visit folder.

*Note 2:* When completing the SVW10001 eCRF in the Maternal Delivery visit folder, answer the questions as you would at any other visit to ensure all appropriate eCRFs become available to you.

For the infant:

The Infant Delivery visit folder is already available for completion under the infant’s PID number. No action is needed to roll out this folder.

**14-P The PKW10002 eCRF collects data on food intake prior to the Delivery and Week 6 Postpartum Visits. Can you clarify the difference between a light snack and a full meal, and the difference between low or moderate fat and high fat? We want to be sure we understand these categories correctly.**

For purposes of this eCRF, a light snack is equivalent to approximately 100 to 300 calories and 1.5 g of fat. For example, this might be a small pudding cup or one slice of toast with jelly and 8 ounces of skimmed milk.

This eCRF originally had three options for fat content: low, moderate, and high. This has been changed to two options: low or moderate fat (combined into one option) and high fat. For purposes of this eCRF, high fat is equivalent to approximately 50% of the total caloric content of the meal.

**14-Q** The Adverse Events Log eCRF (ADE10002) requests a “date EAE first reported to DAERS” in item 12a and a “date of initial report” in item 13. What is the difference between these two dates?

The date requested in item 12a is the date that an adverse event was reported in the DAERS as an EAE. The date requested in item 13 is the date that a log line was added/entered into the ADE100002 eCRF for an adverse event in Rave.

**14-R** The Adverse Events Log eCRF (ADE10002) requests a “DAERS EAE Number” in item 12b. We have a question about this when entering log lines for a diagnosis plus associated signs and symptoms. For example, if we have a case of pneumonia that results in hospitalization. We could have one ADE10002 log line for the diagnosis of pneumonia and several other log lines for signs and symptoms such as fever, chills, shortness of breath. Assuming that one EAE report is submitted into DAERS for this event, would the same DAERS number be entered into item 12b for each of the individual ADE10002 log line entries?

Yes, the same DAERS number would be entered for each of the individual ADE10002 log line entries (this will allow the Protocol Data Managers to link all of the diagnoses, signs, and symptoms to the same adverse event in DAERS).

**14-S** We would like to be sure we understand some queries received for adverse events associated with abnormal laboratory values. For example, we have a postpartum mother at our site who has had grade 3 creatinine values — based on change from baseline — at three consecutive visits. We entered a row in the Adverse Event Log eCRF for “increased creatinine” when the first grade 3 value was obtained. Thereafter, we considered the adverse event ongoing through the next two visits. If we understand correctly now, however, we must enter a new row in the Adverse Event Log eCRF for each grade 3 test value, even though the grade has not changed between tests. Is this correct?

Yes, this is correct. When reporting adverse events associated with abnormal laboratory test results, a new row must be entered into the Adverse Event Log eCRF associated with each individual result.

**Table 14-1**  
**Mapping of Required Maternal History Elements to eCRFs**

<b>Maternal Medical and Medication History Element</b>	<b>eCRF</b>
Date of birth	Subject Enrollment System
Socio-demographics	Subject Enrollment System
HIV diagnosis	MHW10001
WHO clinical staging	EVW10014
Treatment history (including all ARV use prior to enrollment)	CMW10001
Reproductive and obstetrical history <ul style="list-style-type: none"> <li>• Dates and outcomes of all prior pregnancies</li> <li>• Date of last menstrual period prior to the current (index) pregnancy</li> <li>• Medications taken at the time of conception and during the current (index) pregnancy</li> <li>• Complications in the current pregnancy</li> <li>• Other targeted conditions potentially associated with adverse pregnancy outcomes in the current pregnancy</li> <li>• Future fertility intentions and willingness to use effective contraception postpartum (following the current (index) pregnancy)</li> </ul>	<ul style="list-style-type: none"> <li>• OBW10000, LGW10001</li> <li>• EVW10012</li> <li>• CMW10001</li> <li>• DXW10001</li> <li>• DXW10001</li> <li>• Subject Enrollment System</li> </ul>
History of allergy and/or hypersensitivity (including to ARVs)	MHW10001
History of bone fracture (traumatic and non-traumatic)	MHW10001
History of depression and/or suicidality	MHW10001
History of tobacco smoking and alcohol use	HXW10004
Medical conditions (signs, symptoms, illnesses, and other diagnoses) occurring during the 28 days prior to enrollment and/or ongoing at enrollment	MHW10001
Medications taken within the 28 days prior to enrollment and/or ongoing at enrollment	CMW10001
Current status of conditions that were ongoing at the previous visit	MHW10001 if pre-existing condition ADE10002 if adverse event
Occurrence of any new conditions (signs, symptoms, illnesses, and other diagnoses) since the last visit	ADE10002 if meets protocol criteria for eCRF recording
Current status of medications that were ongoing at the previous visit	CMW10001 if concomitant and meets criteria for eCRF recording (in Table 3) TXW10001 if study drug (DTG, FTC/TAF, FTC/TDF, EFV/FTC/TDF)

Maternal Medical and Medication History Element	eCRF
Use of any new medications since the last visit	CMW10001 if concomitant and meets criteria for eCRF recording (in Table 3) TXW10001 if study drug (DTG, FTC/TAF, FTC/TDF, EFV/FTC/TDF)
Complications of index pregnancy identified following enrollment and before delivery, regardless of severity grade	DXW10001
Other targeted conditions potentially associated with adverse index pregnancy outcomes identified following enrollment and before delivery, regardless of severity grade	DXW10001
Date and time of onset of labor for index pregnancy	EVW10015
Type of labor (spontaneous or induced) for index pregnancy	EVW10015
Mode of delivery for index pregnancy	EVW10018
Complications of delivery for index pregnancy	DXW10001
Outcome of delivery for index pregnancy	EVW10013
Whether corticosteroids were taken for fetal lung maturity at any time during index pregnancy	EVW10015 CMW10001 if corticosteroids were taken and meet protocol criteria for eCRF recording (in protocol Table 3)
All contraceptive methods used (postpartum) through completion of follow-up	CMW10001 for methods other than condoms SVW10001 for male and female condom use
Occurrence of subsequent pregnancy	LBW10005 SVW10001
Date of last menstrual period prior to subsequent pregnancy	EVW10012
All medications taken at time of conception and during subsequent pregnancy	CMW10001
All available ultrasound findings during subsequent pregnancy	EVW10012
Subsequent pregnancy outcome	EVW10013



**Table 14-2**  
**Mapping of Required Infant History Elements to the eCRFs**

<b>Infant Medical and Medication History Element</b>	<b>eCRF</b>
Date and time of birth	EVW10018
Sex	EVW10018
Estimated gestational age at birth	Calculated by Protocol Statisticians based on ultrasound findings entered into EVW10012
Length, weight, and head circumference at birth (length, weight, and head circumference measured at the Delivery Visit)	EVW10016 (VSW10001)
Apgar scores at 1 and 5 minutes	EVW10016
Congenital anomalies identified between birth and the Delivery Visit	DXW10000 ADE10002
Other medical conditions (signs, symptoms, illnesses, and other diagnoses) identified between birth and the Delivery Visit	ADE10002 if meets protocol criteria for eCRF recording
Medications taken between birth and the Delivery Visit	CMW10001 if meets protocol criteria for eCRF recording (in protocol Table 4)
Current status of conditions that were ongoing at the previous visit	ADE10002 if meets protocol criteria for eCRF recording
Occurrence of any new conditions (signs, symptoms, illnesses, and other diagnoses) since the last visit	ADE10002 if meets protocol criteria for eCRF recording
Current status of medications that were ongoing at the previous visit	CMW10001 if meets protocol criteria for eCRF recording
Use of any new medications since the last visit	CMW10001 if meets protocol criteria for eCRF recording

## Adverse Event Recording Scenario #1

A mother enrolled with a Grade 1 AST value at screening is found to have an asymptomatic Grade 3 AST value at Antepartum Week 4 (10 May 2018). The Grade 3 value is confirmed (13 May 2018) and the CMC is informed. In consultation with the CMC, the mother's current ART regimen is continued. Upon repeat testing one week later (20 May 2018), a Grade 2 AST value is obtained. One week after that, a Grade 1 AST value is obtained (27 May 2018), and weekly re-evaluation is discontinued. Approximately eight weeks later (25 July 2018), at the Antepartum Week 12 visit, a normal AST value is obtained.

<b>Adverse Events Log ADE10002 Entries for 10 May 2018</b>	<b><i>First log entry for this participant</i></b>
What is the adverse event term?	Increased AST
What is the severity grade of the adverse event?	3
What is the date adverse event started?	10 May 2018
Is the adverse event still ongoing?	[not applicable]
On what date did the adverse event end?	[not applicable]
What is the outcome of the adverse event?	[not applicable]

<b>Adverse Events Log ADE10002 Entries for 13 May 2018</b>	<b><i>Second log entry for this participant</i></b>
What is the adverse event term?	Increased AST
What is the severity grade of the adverse event?	3
What is the date adverse event started?	13 May 2018
Is the adverse event still ongoing?	[not applicable]
On what date did the adverse event end?	[not applicable]
What is the outcome of the adverse event?	[not applicable]

The Grade 2 increased AST value obtained on 20 May 2018 and the Grade 1 increased AST value obtained on 27 May were not serious and did not lead to a change of ART regimen. As such, there would be no entries into the ADE10002 eCRF for these events.

Regardless of requirements for entry into the ADE10002 eCRF, all adverse events must be followed to resolution or stabilization. Therefore, the progression from Grade 3 to Grade 2 to Grade 1 to normal should be fully source documented over time in the mother's study chart.

Also regardless of requirements for entry into the ADE10002, per protocol Section 7.2.1, the Grade 2 AST (20 May 2018) and the Grade 1 AST (27 May 2018) must be entered into the LBW10009 eCRF. The normal AST (25 July 2018) is not required to be entered into the LBW10009 eCRF.

## Adverse Event Recording Scenario #2

At Postpartum Week 6 (10 May 2018), a mother is identified with Grade 2 suicidal ideation. She is provided counseling by study staff and referred for additional follow-up care and treatment from non-study sources. In consultation with the CMC, her current ART regimen is continued. Study staff remain in contact with the participant in the interim prior to her Postpartum Week 14 Visit and, by the date of that visit (10 July 2018), the suicidal ideation has improved to Grade 1. Thereafter, by the date of the mother's Postpartum Week 26 Visit (10 October 2018), the suicidal ideation has resolved; based on the mother's report, resolution occurred on 18 September 2018.

Adverse Events Log ADE10002 Entries for 10 May 2018	First log entry for this participant
What is the adverse event term?	Suicidal ideation
What is the severity grade of the adverse event?	2
What is the date adverse event started?	10 May 2018
Is the adverse event still ongoing?	Yes
On what date did the adverse event end?	[not applicable]
What is the outcome of the adverse event?	[not applicable]

Adverse Events Log ADE10002 Entries for 10 July 2018	First log entry for this participant
What is the adverse event term?	Suicidal ideation ( <b>no change</b> )
What is the severity grade of the adverse event?	2 ( <b>no change</b> )
What is the date adverse event started?	10 May 2018 ( <b>no change</b> )
Is the adverse event still ongoing?	No ( <b>updated entry</b> )
On what date did the adverse event end?	10 July 2018 ( <b>updated entry</b> )
What is the outcome of the adverse event?	Recovering/resolving ( <b>updated entry</b> )

Adverse Events Log ADE10002 Entries for 10 July 2018	Second log entry for this participant
What is the adverse event term?	Suicidal ideation
What is the severity grade of the adverse event?	1
What is the date adverse event started?	10 July 2018
Is the adverse event still ongoing?	Yes
On what date did the adverse event end?	[not applicable]
What is the outcome of the adverse event?	[not applicable]

*Note:* The outcome of the log entry for Grade 2 suicidal ideation will always remain “recovering/resolving.”

<b>Adverse Events Log ADE10002 Entries for 10 October 2018</b>	<b><i>First log entry for this participant</i></b>
What is the adverse event term?	Suicidal ideation <b>(no change)</b>
What is the severity grade of the adverse event?	2 <b>(no change)</b>
What is the date adverse event started?	10 May 2018 <b>(no change)</b>
Is the adverse event still ongoing?	No <b>(no change)</b>
On what date did the adverse event end?	10 July 2018 <b>(no change)</b>
What is the outcome of the adverse event?	Recovering/resolving <b>(no change)</b>

<b>Adverse Events Log ADE10002 Entries for 10 October 2018</b>	<b><i>Second log entry for this participant</i></b>
What is the adverse event term?	Suicidal ideation <b>(no change)</b>
What is the severity grade of the adverse event?	1 <b>(no change)</b>
What is the date adverse event started?	10 July 2018 <b>(no change)</b>
Is the adverse event still ongoing?	No <b>(updated entry)</b>
On what date did the adverse event end?	18 September 2018 <b>(updated entry)</b>
What is the outcome of the adverse event?	Recovered/resolved <b>(updated entry)</b>

### Adverse Event Recording Scenario #3

At Antepartum Week 12 (10 May 2018), a mother is identified with Grade 3 pre-eclampsia and is admitted for inpatient monitoring and treatment. Five days later, study staff are informed that the mother's condition deteriorated in hospital (on 14 May 2018) and she died that day.

Adverse Events Log ADE10002 Entries for 10 May 2018	First log entry for this participant
What is the adverse event term?	Pre-eclampsia
What is the severity grade of the adverse event?	3
What is the date adverse event started?	10 May 2018
Is the adverse event still ongoing?	Yes
On what date did the adverse event end?	[not applicable]
What is the outcome of the adverse event?	[not applicable]

Adverse Events Log ADE10002 Entries for 15 May 2018	First log entry for this participant
What is the adverse event term?	Pre-eclampsia ( <b>no change</b> )
What is the severity grade of the adverse event?	3 ( <b>no change</b> )
What is the date adverse event started?	10 May 2018 ( <b>no change</b> )
Is the adverse event still ongoing?	No ( <b>updated entry</b> )
On what date did the adverse event end?	14 May 2018 ( <b>updated entry</b> )
What is the outcome of the adverse event?	Not recovered/not resolved ( <b>updated entry</b> )

Adverse Events Log ADE10002 Entries for 15 May 2018	Second log entry for this participant
What is the adverse event term?	Pre-eclampsia
What is the severity grade of the adverse event?	5
What is the date adverse event started?	14 May 2018
Is the adverse event still ongoing?	No
On what date did the adverse event end?	14 May 2018
What is the outcome of the adverse event?	Fatal

*Note:* The outcome of the log entry for Grade 3 pre-eclampsia will always remain “not recovered/not resolved.”

## Adverse Event Recording Scenario #4

Between Postpartum Weeks 38 and 50, a mother is hospitalized. After two days in hospital, her husband informs study staff of the hospitalization. On the day of this contact, 12 May 2018, a study clinician visits the hospital and obtains sufficient information to assess the pneumonia as potentially life-threatening. The next day, the clinician learns that the mother has developed a moderate rash and her antibiotics were changed because of this. Three days later, the rash has resolved and the pneumonia has improved somewhat. Two days after that, the pneumonia has improved further, and the mother is discharged home. Based on full review of the mother's hospital records on 20 May 2018, the study clinician determines the following:

- Admission occurred on 10 May 2018. Prior to that, symptoms of pneumonia began on 3 May 2018.
- Grade 4 pneumonia improved over the course of the hospitalization and was Grade 2 at discharge on 18 May 2018.
- Grade 2 rash began on 13 May 2018 and was resolved on 16 May 2018.

Adverse Events Log ADE10002 Entries for 12 May 2018	First log entry for this participant
What is the adverse event term?	Pneumonia
What is the severity grade of the adverse event?	4
What is the date adverse event started?	[best available date at time of eCRF entry]
Is the adverse event still ongoing?	Yes
On what date did the adverse event end?	[not applicable]
What is the outcome of the adverse event?	[not applicable]

Adverse Events Log ADE10002 Entries for 20 May 2018	First log entry for this participant
What is the adverse event term?	Pneumonia <b>(no change)</b>
What is the severity grade of the adverse event?	4 <b>(no change)</b>
What is the date adverse event started?	3 May 2018 <b>(updated entry)</b>
Is the adverse event still ongoing?	No <b>(updated entry)</b>
On what date did the adverse event end?	18 May 2018 <b>(updated entry)</b>
What is the outcome of the adverse event?	Recovering/resolving <b>(updated entry)</b>

*Note:* Further follow-up will be required to follow the pneumonia to resolution. However, the outcome of the log entry for this event will always remain “recovering/resolving.”

Adverse Events Log ADE10002 Entries for 20 May 2018	Second log entry for this participant
What is the adverse event term?	Rash
What is the severity grade of the adverse event?	2
What is the date adverse event started?	13 May 2018
Is the adverse event still ongoing?	No
On what date did the adverse event end?	16 May 2018
What is the outcome of the adverse event?	Recovered/resolved