Eligibility Criteria

1. **Question:** Can the team clarify how to determine maternal eligibility in terms of age? The protocol specifies 16-24 years of age; however, we are unsure of the cut off point for the upper age limit.

**Answer:** Maternal participants can enroll up to the day of their 25th birthday (i.e., 24 years 364 days of age).

2. **Question:** How should gestational age be calculated in the event that the 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?

**Answer:** Inclusion criterion 4.1.1.3 requires that mothers in Group 1 be enrolled at 14-24 weeks gestation, which is defined as greater than 13 weeks plus six days and less than 24 completed weeks of gestation with sonographic confirmation.

The published American College of Obstetricians and Gynecologists (ACOG) method for determining gestational age, 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: https://www.acog.org/About-ACOG/News-Room/ACOG-App.

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 the clarifications to protocol Section 6.15 implemented in Clarification Memorandum (CM) #1, ultrasound result reports should include the following:

- Date of scan
- Number of fetuses
- Biometry measures for
  - **If ≤ 14 weeks gestation:**
    - Crown-rump length
  - **If > 14 weeks gestation:**
    - Femur length, abdominal circumference, and either or both head circumference and biparietal diameter
- Calculated gestational age on the date of the scan or estimated date of delivery

**Note:** Sites are responsible for entering the above-listed ultrasound findings into eCRFs. Although the protocol allows for either head circumference or biparietal diameter to be entered (if 14 or more weeks gestation), both of these measurements should be entered whenever available.

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 the ACOG method, or determining eligibility based on gestational age for any potential participant.

3. **Question:** Per exclusion Criterion 4.1.2.10, mothers must be excluded from the study if they have had past participation in IMPAACT 2009; would this prohibit mothers who participated for a period of time and then had a break in participation or who move from re-enrolling in the study?

**Answer:** If a participant has a break in study participation and is considered lost to follow-up or is otherwise withdrawn from the study she cannot re-enroll. If a participant moves, every effort should be made to either: a) continue her participation at the current site if logistically possible, or b) transfer her to another participating site. If she cannot continue participation at her original site or be transferred to another site, she would need to be withdrawn and could not re-enroll.

A participant cannot enroll into both groups in the PK Component nor can she enroll into the both PK component and the PrEP Comparison Component (regardless of whether or not she completes follow-up after her initial enrollment).

### Accrual, Recruitment, Screening, Enrollment, and Retention

4. **Question:** Is there a protocol-defined standardized HIV risk assessment?

**Answer:** The protocol does not require a specific HIV risk assessment tool. Protocol Section 4.5, Recruitment, Screening, and Enrollment Process, states that: “Women at heightened risk of HIV acquisition will be recruited for the PK Component and PrEP Comparison Component from public health centers where standard of care HIV pre-and post-test counseling procedures include a standardized HIV risk assessment. Study staff will approach women who, based on this risk assessment, perceive themselves to be at heightened risk and express interest in learning more about methods to protect themselves [emphasis added].” Sites should rely on standard of care HIV risk assessment processes and procedures currently in place in locations from which they will recruit potential participants.

### Adverse Event Reporting

5. **Question:** How should laboratory test results that constitute Adverse Events (AEs) be reported on eCRFs?

**Answer:** Laboratory test results that meet the protocol defined criteria for entry into AE eCRFs should be entered on both forms; see protocol Sections 7.2.1 and 7.2.2. For example:

<table>
<thead>
<tr>
<th>Event</th>
<th>Enter Value in Laboratory eCRF?</th>
<th>Enter Adverse Event eCRF?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 creatinine</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Grade 2 creatinine</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Grade 3 creatinine</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Grade 4 creatinine</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
6. **Question:** For an isolated asymptomatic Grade 3 or Grade 4 laboratory AE, should the site conduct a repeat test first or do they have to inform the CMC?

**Answer:** Refer to protocol Appendices IV and V; in general, sites should repeat the test to confirm the severity before alerting the CMC. When sending a query to the CMC, follow the formatting guidance in the IMPAACT 2009 Manual of Procedures regarding the content and subject of the message.

<table>
<thead>
<tr>
<th>Event</th>
<th>Enter Value in Laboratory eCRF?</th>
<th>Enter Adverse Event eCRF?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 hemoglobin</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Grade 2 hemoglobin</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Grade 3 hemoglobin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Grade 4 hemoglobin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

7. **Question:** Does an asymptomatic Grade 4 lab abnormality automatically qualify as a Serious Adverse Event (SAE)?

**Answer:** Not necessarily – if the event does not meet the definition of the SAE reporting category (Appendix A) as defined in the DAIDS Manual for Expedited Reporting of Adverse Events, Version 2.0. For example, if lab results indicate a Grade 4 ALT yet the participant is asymptomatic, does not require hospitalization, and the event is deemed non-life threatening, this event may not meet the criteria to be considered an SAE. This participant should be carefully followed and managed per the guidelines in protocol Section 8 and Appendix IV.

8. **Question:** Do suggested congenital anomalies require EAE reporting?

**Answer:** Refer to protocol Sections 7.2 and 7.3. Suspected congenital anomalies are recorded in the participant’s source file and entered as an infant AE on the respective eCRF. If the anomaly meets the criteria for a serious AE, then it would meet the reporting criteria for expedited reporting.

### Participant Management

9. **Question:** Protocol Appendices IA and IIA specify that 1mL blood draw for random glucose must be drawn at Screening; however, results of this test are not required for participant eligibility determination. Please clarify if/where the results of this test should be entered into the study database, and how clinical management should be handled if abnormal results are obtained?

**Answer:** If there is an abnormal result, participants should be referred to the appropriate standard of care at the site for further evaluation. Depending on the severity of the abnormality, and judgement of the site investigators, the team may also exclude the participant from further participation based on exclusion criterion 4.1.2.9. As with other laboratory test results obtained at screening, normal random glucose results would not be required to be entered into the study database; abnormal results would be entered only if they meet the requirements specified in protocol Section 7.2.
10. **Question:** Does the Entry visit require two separate blood draws for the HIV rapid test and other laboratory tests? For sites that have separate screening and enrollment consent forms, how should the rapid HIV test required within at entry be handled?

**Answer:** No, it is expected that the blood collected for other tests at Entry may also be used for the rapid HIV test. If the HIV rapid test is positive, enrollment should not occur and the procedures in protocol Section 6.16 should be followed. For sites that have separate screening and enrollment consent forms, this blood collection should occur after the participant has signed the enrollment consent form. For IMPAACT 2009, the point of enrollment is when the participant’s eligibility is confirmed via the Subject Enrollment System (i.e. not when the participant signs the informed consent forms).

11. **Question:** Why is pregnancy testing performed at Week 12 (i.e. Study Exit) for Group 2 mothers?

**Answer:** Per protocol Section 8.2., participants who are pregnant at the time of study exit, will be contacted by study staff to ascertain their pregnancy outcomes (completion/termination of the pregnancy; this information will be entered into eCRFs).

12. **Question:** Is an additional consent required for participants who become pregnant on study?

**Answer:** The protocol does not require additional consent for participants who become pregnant on study, and sites should follow their IRB/EC policies and procedures regarding informed consent requirements. See protocol Section 8.2 for additional guidance on management of participants who become pregnant on study.

13. **Question:** Will the results of HIV drug resistance testing be shared with participants in the event that a maternal participant seroconverts during study follow-up?

**Answer:** Yes. Per protocol Section 13.5.5, if a participant becomes HIV infected during the study, the site will obtain real-time resistance testing for clinical management. Sites should share the results of this testing with the participant.

14. **Question:** Will HIV resistance testing be conducted for infants?

**Answer:** Yes, for infants who are confirmed HIV-infected, 1.5 mL of blood will be collected for non-viable PBMCs to test for resistance at the confirmatory visit and every study visit thereafter, if applicable; refer to protocol Section 6.3.4 and Appendix IIE.

15. **Question:** The protocol clearly states that for the baseline TFV-DP level (DBS) at the enrollment visit, the blood sample should be drawn prior to ingestion for study drug. Please advise if we are required to have blood samples for the subsequent TFV-DP level (DBS) to be drawn before the dose of that visit is ingested.

**Answer:** The blood sample for the TFV-DP level (DBS) must be drawn prior to ingestion of study drug only at the enrollment visit to establish a baseline; there are no requirements for the timing of collection relative to dosing for subsequent visits.
16. Question: Can you explain the maternal and infant visit schedule following an initial positive maternal HIV test?

**Answer:** An overview of the study visit schedule following an initial positive maternal HIV test for participants in the PK Component is presented here. Protocol Section 6.3 should be carefully followed for detailed guidance on management of participants with suspected or confirmed HIV seroconversion.

**Maternal Participants:**

**Confirmatory Visit:**
For maternal participants who have an initial positive HIV test, **PrEP should be immediately stopped**, and additional Confirmatory Visit procedures should be performed as indicated in protocol Section 6.3.1 and Appendix IID. Confirmatory testing should be performed according to the site’s HIV testing algorithm.

In general, if the initial test indicating infection is a rapid HIV test, additional Confirmatory Visit procedures should be performed on the same day as the initial test; if the initial test indicating infection is an HIV-1 RNA test, the participant should be contacted immediately upon receipt of the test result to advise her to stop PrEP and request that she return to the clinic for confirmatory HIV testing and other required Confirmatory Visit procedures as soon as possible (within two business days). The Confirmatory Visit can be combined with other scheduled study visits if conducted within the allowable window.

**Confirmed Infected – Visit 4 weeks after date of initial HIV positive blood draw:**
Maternal participants with confirmed HIV infection should be scheduled for a visit to occur four weeks after the date of the blood draw for the initial positive HIV test. This visit is **in addition to scheduled visits** and can be combined with a scheduled visit if conducted within the allowable window. This will be the final study visit for maternal participants in the PK Component.

**Infants:**

**Confirmatory Testing:**
Infants of women diagnosed as HIV-infected **during pregnancy** should undergo HIV nucleic acid testing (NAT) as soon as possible after birth. Infants of women diagnosed **after delivery** should undergo HIV NAT on the day that the mother undergoes confirmatory HIV testing.

**Subsequent Study Visits:**
Infants of women diagnosed as HIV-infected (during pregnancy or post-partum) will **remain on study through his or her scheduled study exit** for safety monitoring, even if this extends beyond maternal participants final study visit.

Following the initial confirmatory testing, the infant visit schedule does not change, however, additional procedures are to be performed at study visits as indicated in Appendix IIE.

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**Data Management**

17. Question: During the IMPAACT 2009 Data Management Considerations webinar, it was noted that when completing the Adverse Events Log (ADE 10000), specifically question #9 - **Is the Adverse Event related to study treatment?** - sites should always choose “not applicable” for infants, as they have no study treatment; however, we are not sure if this is always the case as some infants will be exposed in-utero or through breastmilk.
**Answer:** Protocol Section 7.3.4 states: “For infants, exposure to study drug may occur in utero and/or through breast milk while the mother is taking FTC/TDF. The EAE reporting period begins on the day of the first exposure in utero or through breast milk and ends after the day of last exposure in utero or through breast milk,” therefore there may be situations where determination of AE relationship to study treatment will be required for infants, and this will be entered into eCRFs accordingly.

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**Integrated Next Step Counseling (iNSC)**

18. **Question:** Is there a required tracking document for iNSC sessions?

**Answer:** Per protocol, there are no specific documentation requirements for the iNSC sessions. From a data management perspective, the only eCRF requirement related to iNSC is that sites indicate “Yes” or “No” for the question “Was iNSC administered at this visit?” when completing Form: SVW10010 (IMPAACT 2009 PK Component – Maternal Study Event Tracking). Sites are welcome, but not required, to use the sample iNSC tracking form that was reviewed at the regional training. This resource may be adapted for use in your local setting, and is available on the study-specific webpage: [https://impaactnetwork.org/studies/IMPAACT2009_trainings.htm](https://impaactnetwork.org/studies/IMPAACT2009_trainings.htm).