Summary of Changes Included in the Full Protocol Amendment of:

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

The Amended Protocol is Identified as:

Version 2.0, dated 8 December 2017
DAIDS Study ID #30129
IND #133,438

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Information/Instructions to Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the IMPAACT 2010 study, including the study informed consent forms (ICFs), and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon obtaining all required IRB/EC approvals and any other applicable regulatory entity approvals, each site should immediately begin implementing this amendment, using site-specific Version 2.0 ICFs when obtaining informed consent for mother-infant pairs enrolled under protocol Version 2.0. For mothers and infants enrolled under Version 1.0, re-consent for study participation should be obtained using the site-specific ICFs for protocol Version 2.0; unless otherwise determined by site IRBs/ECS or other regulatory entities, re-consent for specimen storage and future research use is not required.

Upon receiving IRB/EC approvals and any other applicable regulatory entity approvals, all sites are required to submit an amendment registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will then receive a registration notification for the amendment after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this amendment. Modified study procedures that are applicable across all sites, including removal of the participant accrual cap and updated routine safety monitoring procedures, will be implemented immediately upon issuance of this amendment.
Please file this Summary of Changes, Version 2.0 of the protocol, corresponding site-specific ICFs, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT 2010.

### Summary and Rationale

The main purpose of this amendment is to implement protocol modifications recommended by the United States (US) Food and Drug Administration (FDA) and the National Institute of Allergy and Infectious Diseases (NIAID) Data and Safety Monitoring Board (DSMB) responsible for oversight of the study. This amendment also incorporates information about the study drugs that became available after protocol Version 1.0 was finalized, as well as clarifications provided in Clarification Memoranda issued under protocol Version 1.0.

Modifications incorporated into the protocol are summarized as follows:

- The primary study objective related to virologic efficacy at delivery was originally specified to determine whether treatment initiated during pregnancy with a dolutegravir (DTG) containing regimen is superior to efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF). This has been modified to determine whether a DTG-containing regimen is non-inferior to EFV/FTC/TDF. Superiority will still be assessed, but as a secondary objective. To accommodate this modification of the primary objective, the study sample size has been increased to 639 mother-infant pairs (213 pairs per study treatment arm).

- The secondary study objectives have also been updated to include evaluation of whether the following differ when comparing a DTG-containing regimen to EFV/FTC/TDF:
  - Time to HIV-1 RNA suppression to less than 200 copies/mL through delivery
  - Rate of adverse pregnancy outcomes and maternal and infant grade 3 or higher adverse events

- The previously-specified cap on the monthly rate of participant accrual has been eliminated from the protocol. In lieu of this cap, DSMB reviews of participant safety outcomes by study treatment arm have been specified to occur every six months.

- The previously-specified role of the Clinical Management Committee (CMC) in reviewing participant safety outcomes pooled across study treatment arms has been eliminated from the protocol and assigned instead to a Safety Review Group that will include the Protocol Medical Officers, Protocol Statisticians, Protocol Data Managers, and other reviewers who are independent of the Protocol Team.

- The background sections of the protocol have been updated to include information about the study drugs that became available after protocol Version 1.0 was finalized. In addition, information about the pharmacokinetics (PK) of tenofovir alafenamide (TAF) in pregnancy, which was previously provided in protocol Version 1.0 Clarification Memorandum (CM) #1, has been incorporated into the protocol. Other clarifications previously provided in protocol Version 1.0 CM #2 have also been incorporated.
- The study eligibility criteria have been updated to clarify that HIV-2 infection and antiretroviral (ARV) drug resistance mutations that would impact selection of a maternal participant’s ARV regimen are exclusionary, whereas prior use of tenofovir disoproxil fumarate (TDF) or emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) for pre-exposure prophylaxis is not exclusionary.

- The study drug supply section of the protocol has been updated to include operational guidance on consultation with the CMC regarding ART regimen changes and to specify operational requirements for use of non-study-supplied ARVs as part of study ART regimens.

- The procedural sections of the protocol have been updated to provide further operational guidance with respect to target visit dates and allowable visit windows. For Delivery Visits, both a targeted visit window and an allowable visit window have been specified.

- The procedural sections of the protocol have been updated to clarify when standardized questionnaires pertaining to sleep and anxiety are administered and to specify that ARV resistance testing will be performed in real-time for maternal participants who experience virologic failure. These sections have also been updated to clarify when selected laboratory tests should be performed for infants who have or have not been exposed to breast milk.

- The statistical section of the protocol has been updated as needed to reflect modifications of the study objectives and all applicable study design and analysis considerations. Consistent with current requirements for submitting study results to ClinicalTrials.gov, the outcome measures specified in this section have been categorized as primary, secondary, other, and exploratory.

- The sample informed consent form for mother-infant pair study participation has been updated to reflect the current study drug Package Inserts and to reflect all other protocol modifications.

- The protocol team and study site rosters have been updated to reflect current membership. References have been updated and other administrative updates and corrections have been incorporated throughout the protocol for accuracy, consistency, and clarity. The table of contents has been updated to reflect current protocol sections and page numbers and to include lists of tables and figures.

**Implementation**

Modifications of protocol text are described in two sections below. The first section includes modifications newly introduced in protocol Version 2.0. The second section includes updates, clarifications, and minor corrections first introduced in protocol Version 1.0 CM #2. Within each section, modifications are generally listed in order of appearance in the protocol. Where applicable, modified protocol text is shown using strikethrough for deletions and bold type for additions.


**Modifications Introduced in Protocol Version 2.0**

1. The amended protocol is identified as FINAL Version 2.0, dated 8 December 2017. A protocol signature page has been added. The table of contents, abbreviation and acronym list, reference list, and protocol team and study site rosters have been updated.

2. In the Schema, Figure 1, and throughout the protocol, the study sample size has been increased to 639 mother-infant pairs (approximately 213 per arm).

3. In the Schema and Section 2, the first primary objective has been modified to evaluate non-inferiority and the first secondary objective has been modified to evaluate superiority:

   2.1.1 Whether treatment initiated during pregnancy with a DTG-containing regimen is superior non-inferior to EFV/FTC/TDF with regard to virologic efficacy (HIV-1 RNA <200 copies/mL) at delivery

   2.2.1 Whether treatment initiated during pregnancy with a DTG-containing regimen is non-inferior superior to EFV/FTC/TDF with regard to virologic efficacy (HIV-1 RNA <200 copies/mL) at delivery

Section 1.9.2 has been modified to specify the rationale for evaluating non-inferiority as part of the primary virologic efficacy objective; Section 1.10 has been modified to specify the hypothesis associated with this objective; and the sample size increase noted above has been incorporated to provide adequate statistical power for this objective. Section 9 has been modified (throughout) to reflect study design and statistical considerations associated with the modified primary and secondary objectives.

4. In the Schema and Section 2, secondary objectives have been added as follows:

   2.2.2 Whether the following differ when comparing a DTG-containing regimen initiated during pregnancy to EFV/FTC/TDF:
   - Proportion of mothers with HIV-1 RNA <50 copies/mL at delivery
   - Proportion of mothers with HIV-1 RNA <200 copies/mL at 50 weeks postpartum
   - Time to maternal HIV-1 RNA <200 copies/mL through delivery

   2.2.4 Whether rates of the following differ when comparing a DTG-containing regimen to EFV/FTC/TDF:
   - Adverse pregnancy outcomes (spontaneous abortion, fetal death, preterm delivery, or small for gestational age)
   - Maternal grade 3 or higher adverse events through 50 weeks postpartum
   - Infant grade 3 or higher adverse events through 50 weeks postpartum

5. Section 1.1 was modified to reflect that data on use of DTG and TAF are emerging, as described in greater detail in Sections 1.2.2 and 1.3.2.

6. Sections 1.2.1 and 1.2.2 were modified to incorporate updated information from studies of DTG in non-pregnant adults and in pregnancy, respectively.
7. Section 1.3.2 was modified to incorporate updated information from studies of TAF in pregnancy and to document the review of TAF pregnancy PK data that took place prior to opening the study to accrual under protocol Version 1.0.

8. Section 1.4 was modified to incorporate updated information from studies of DTG/3TC as two-drug initial therapy in ART-naïve adults.

9. Section 1.9.6 was modified to note that, in addition to maternal postpartum depression, this study will assess sleep disturbances and anxiety.

10. Section 3 has been modified to reflect removal of the cap on participant enrollment that was specified in protocol Version 1.0. Section 9.4, which describes participant accrual, has also been modified accordingly.

11. Inclusion criterion 4.1.3 and exclusion criterion 4.2.4 (seventh bullet point) have been modified to clarify that use of ARVs for pre-exposure prophylaxis is not exclusionary, as follows:

   4.1.3 At screening, mother is ART-naïve, defined as having not received prior antiretroviral therapy other than ARVs received during prior pregnancies or prior periods of breastfeeding (i.e., receipt of any single, dual, or triple ARV regimen during prior time-limited periods of pregnancy and breastfeeding is permitted). Receipt of up to 14 days of ARVs during the current pregnancy is permitted prior to study entry so that initiation of ARVs during the current pregnancy is not delayed during the study screening period.

   Note: Non-study ART may be initiated in the current pregnancy prior to initiation of the study screening process. For eligible participants, enrollment must occur within 14 days of non-study ART initiation.

   Note: Consistent with criterion 4.2.4, receipt of ARVs during a prior pregnancy or prior period of breastfeeding must have concluded at least six months prior to study entry. Receipt of TDF or FTC/TDF for pre-exposure prophylaxis at any time in the past is not exclusionary (even if received within six months prior to study entry).

   4.2.4 Mother has a history of any of the following, as determined by the site investigator or designee based on maternal report and available medical records:

   • Receipt of any antiretroviral medication within six months prior to study entry, with the exception of two exceptions: receipt of any duration of TDF or FTC/TDF for pre-exposure prophylaxis or receipt of up to 14 days of ARVs during the current pregnancy

12. Exclusion criterion 4.2.4 (second bullet point, added) has been modified to exclude mothers with known resistant virus, as follows:

   4.2.4 Mother has a history of any of the following, as determined by the site investigator or designee based on maternal report and available medical records:

   • Antiretroviral drug resistance mutations that would impact selection of ART regimen (ever)
13. Exclusion criterion 4.2.4 (fifth bullet point, added) has been modified to exclude mothers with known HIV-2 infection, as follows:

4.2.4  Mother has a history of any of the following, as determined by the site investigator or designee based on maternal report and available medical records:

- HIV-2 infection

14. Section 5.1 has been modified to clarify the expected timing of the first dose of study drug, with the following addition:

As noted in Section 4.4, the first dose of each regimen is expected to be taken on the day of enrollment or the following day.

15. In Section 5.4, the fifth and sixth paragraphs have been modified to provide further guidance related to maternal ART regimen changes and use of non-study-supplied ARVs, as follows:

Study-supplied study drugs are expected to be provided to mothers in Arms 1, 2, and 3 consistent with their random assignments as specified in Section 5.1. However, for mothers in all arms, maternal ART regimens may be modified as specified in Section 8 and Appendix II. As indicated in these sections, all regimen changes involving DTG, EFV, TAF, or TDF should be made in consultation with the CMC.

All available study-supplied study drugs, as well as ARVs available from non-study sources, may be used when constructing regimens for mothers in all arms. In the event that study supplies of DTG, FTC/TAF, FTC/TDF, or EFV/FTC/TDF are not available, these ARVs may be provided from non-study supplies, with approval in advance from the CMC. If non-study-supplied ARVs are provided, the ARVs should ideally be dispensed through study site pharmacies. If this is not possible, other options may be considered in consultation with the CMC; CMC review and approval of the operational plan is required. Any ARV supplied from non-study sources must comply with the DAIDS policy on use of drug products not marketed in the US, which is available at: https://www.niaid.nih.gov/research/daids-clinical-research-pharmacy-and-study-products-management.

16. In Section 6, the second paragraph has been modified to provide further guidance related to study visit target dates and visit windows, as follows:

All visits and procedures must be performed at the approved clinical research site or approved associated facilities. All visits should be conducted as close as possible to the specified target visit dates and within the specified allowable visit windows. Unless otherwise specified, visits may be split, with required procedures performed on more than one day within the allowable visit window if necessary. Some visit windows overlap by a period of one day; the day of overlap should be prioritized, when applicable, for completion of the earlier of the two visits. For example, there is one day of overlap between the allowable windows for the Antepartum Week 4 and Week 8 Visits. If a participant were to present to the study site on this day, the Antepartum Week 4 Visit should be conducted on this day, if not previously conducted; otherwise, the Antepartum Week 8 Visit may be conducted on this day. In the event that a scheduled visit is missed (i.e., not completed within the allowable window), 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 on prioritization of evaluations is provided in the study-specific MOP.

All visits and procedures must be documented in accordance with the NIAID Division of AIDS (DAIDS) policies for source documentation; refer to Section 10 for more information on documentation and data management requirements. Refer to Section 7 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up.

17. Section 6.2 has been modified to clarify the expected timing of blood collection at the Entry Visit, as follows:

Blood collection should ideally precede enrollment and must precede ingestion of the first dose of study drug.

18. In Sections 6.2, 6.3.2, and 6.5.4, the Clinical row in each maternal procedural table is updated to include administration of the Pittsburgh Sleep Quality Index (PSQI) and Generalized Anxiety Disorder 7-Item Scale (GAD-7) at the Study Entry, Antepartum Week 8, and Postpartum Week 38 Visits. Similarly, in Section 6.6, the Clinical row in the maternal procedural table is updated to include administration of the PSQI, GAD-7, and Edinburgh Postnatal Depression Scale (EPDS) at Post Maternal ARV Switch Visits. The Schedule of Evaluations in Appendix I is also updated to specify administration of these standardized questionnaires, as is the sample informed consent form in Appendix III.

19. In Sections 6.3-6.7 and 6.9, the Study Drug row in each maternal procedural table is updated to clarify requirements for administration of adherence questionnaires. A routine adherence questionnaire is administered at all visits and a barriers and facilitators questionnaire is administered at the Antepartum Week 8 and Postpartum Week 38 Visits. The Schedule of Evaluations in Appendix I is also updated to clarify these requirements. In addition, at the Delivery and Postpartum Week 6 Visits, details of the last two ARV doses will be collected.

20. Sections 6.4, 6.14, and 9.5.1 and the Schedule of Evaluations in Appendix I are updated to describe targeted and allowable visit windows for maternal and infant Delivery Visits.

In Section 6.4, the first and second paragraphs are updated as follows:

Mothers and infants should complete a study visit as soon as possible after delivery, and within a targeted window of 14 days after delivery.

In addition to other evaluations, the primary study outcomes are ascertained at this visit. As such, every effort should be made to conduct this visit within the targeted window. If the visit cannot be conducted within the targeted window, it may be conducted within an allowable window of 27 days after delivery. The timeliness of visit completion at each site will be closely monitored and corrective actions taken when needed, as described in Section 9.5.1.

The procedural table headings in Section 6.4 and the Schedule of Evaluations are also updated to reflect the targeted and allowable visit windows.
In Section 6.14, the second paragraph is updated as follows:

The infant baseline medical and medication history will consist of information recorded at birth as well as information obtained at the Delivery Visit. The Delivery Visit should take place as soon as possible after birth, but may take place up to 14 days after birth; as and within the targeted window of up to 14 days after birth; if the visit cannot be conducted within the targeted window, it may be conducted within the allowable window of up to 27 days after delivery. As such, information recorded at birth may differ from information obtained at the Delivery Visit.

In Section 9.5.1, the following is added to the end of the last paragraph:

The CMC will also monitor the timeliness of maternal and infant Delivery Visits at each site in a similar manner. Sites that do not consistently complete these visits within the targeted window will be required to implement appropriate corrective action plans; consideration may also be given to pausing accrual at such sites while corrective action is being taken.

21. In Section 6.4, the Laboratory/Blood row in the maternal and infant procedural tables are updated to clarify expectations for Zika virus testing, as follows:

- 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: stored serum for Zika diagnostic testing

The Schedule of Evaluations in Appendix I is also updated to reflect this clarification.

22. In Sections 6.4 and 6.5, the Laboratory/Blood row in each infant procedural table is updated to clarify that all remnant sample types remaining after HIV nucleic acid testing (NAT) has been performed should be stored, as follows:

- HIV NAT (store residual plasma remnant samples)

Section 6.8 and the Schedule of Evaluations in Appendix I are also updated to clarify this expectation for specimen storage.

23. In Sections 6.5.3 and 6.5.4, the Laboratory/Blood row in each infant procedural table is also updated to specify that HIV NAT is required at the Week 26 and Week 38 Visits for infants ever exposed to breast milk (for infants never exposed to breast milk, HIV NAT is not required at these visits).

In Section 6.5.3, the Laboratory/Blood row in the infant procedural table is similarly updated to specify that chemistry and hematology testing (ALT, creatinine, complete blood count) is required at the Week 26 visit only for infants ever exposed to breast milk.

Footnote 7 and footnote 9 (newly added) in the Schedule of Evaluations in Appendix I (Delivery and Postpartum) are also updated to clarify these expectations for laboratory testing.
24. In Sections 6.7, 6.18.2, and 8.3, and in the Schedule of Evaluations in Appendix I, procedural requirements for maternal participants with virologic failure are modified to specify that ARV resistance testing will be performed in real-time, as follows:

Section 6.7, Laboratory/Blood row of procedural table
Collect blood for:
- HIV-1 RNA (real-time; store residual plasma)
- Stored plasma for Antiretroviral resistance testing (real-time if virologic failure is confirmed, with storage of residual plasma; otherwise store plasma)

Section 6.18.2, second, third, and fourth paragraphs
At each study site, all maternal plasma HIV-1 RNA assays must be performed in real time in a VQA-certified laboratory using the testing platform specified in the LPC. For mothers who experience virologic failure, antiretroviral resistance testing will be performed in real time at designated VQA-certified laboratories. Blood collected for resistance testing at Confirmation of Virologic Failure Visits will be processed locally, with plasma retained at the site laboratory pending HIV-1 RNA testing to confirm virologic failure. If failure is confirmed, aliquots of plasma stored for resistance testing at the Screening Visit and the Confirmation of Virologic Failure Visit will be shipped to a designated VQA-certified testing laboratory (residual plasma aliquots will be stored at the site laboratory); if failure is not confirmed, all plasma aliquots will remain stored at the site laboratory.

Infant HIV NAT must be performed in a VQA-certified laboratory (for non-US sites) or a CLIA-certified laboratory (for US sites). Whenever these tests are performed, any plasma remaining after the assay is completed should be stored.

Most specimens collected and stored at site laboratories per the Schedule of Evaluations are expected to be requested for centralized testing after all participants have completed follow-up (through Week 50 postpartum). However, an interim shipment is planned when all enrolled mothers have delivered. At this time, all specimens stored for centralized HIV-1 RNA testing and all specimens stored for resistance testing will be requested for shipment to the designated testing laboratory. These specimens will then be tested as needed to evaluate outcomes through the delivery time point.

Section 8.3

Confirmation of Virologic Failure

Any mother with a plasma HIV-1 RNA level ≥200 copies/mL at or after 24 weeks on study should be recalled to the clinic for confirmatory testing as soon as possible and within 28 days of the date of specimen collection for the initial test. As indicated in Section 6.7, other evaluations — including specimen collection for resistance testing — will also be performed at the time of specimen collection for confirmatory HIV-1 RNA testing. All procedures should be performed regardless of reported adherence to study drug or any other factors that may affect HIV-1 RNA results.
**Management of Confirmed Virologic Failure**

The CMC should be consulted regarding management of all participants with confirmed virologic failure.

For mothers with confirmed virologic failure, upon receipt of the confirmatory HIV-1 RNA test result, specimens collected for antiretroviral resistance testing at the Screening Visit and the Confirmation of Virologic Failure Visit should be shipped to a designated VQA-certified testing laboratory. Resistance test results will be provided in real time to help guide ART regimen management, as described below.

If the virologic failure is assessed as likely due to non-adherence, the current study drug ART regimen may be continued, with enhanced adherence support per site SOPs (see Section 5.7) and continued virologic monitoring. Likewise, if the failure is assessed as due to intercurrent illness or other factors not associated with the current study drug regimen, the current regimen may be continued. Otherwise, the regimen should generally be modified in consultation with the CMC. Recommendations for alternative regimens should take into consideration the participant’s preferences and medical history, current regimen, and current local standard guidelines for first- and second-line regimens, and resistance test results. For any mother whose regimen is modified such that DTG or EFV is replaced with another ARV, an additional study visit should be conducted approximately four weeks after the switch as described in Section 6.6.

25. In Section 6.8, first paragraph, procedural requirements for infants with positive HIV NAT results are modified to include specimen collection for ARV resistance testing at the time of confirmatory testing, as follows:

Any infant with a positive HIV NAT result should be recalled to the clinic for confirmatory testing as soon as possible and within 28 days of specimen collection for the initial test. As is the case at other visits when HIV NAT is performed, 3 mL of blood should be collected for the testing and plasma remnant samples will be stored; an additional 3 mL should also be collected and stored for antiretroviral resistance testing. In the event that the second test does not confirm the initial result, the CMC should be consulted for guidance on next steps to clarify the infant’s HIV status. Pending confirmatory testing, infant prophylaxis ARVs should be managed consistent with local standards of care.

26. In Section 6.10, first paragraph, documentation requirements for post-study contacts are modified as follows:

As indicated in Sections 6.5.4 and 6.5.5, planning for transition to non-study care and treatment should begin at the Week 38 Visit, and the transition should be implemented at the Week 50 Visit. Following the Week 50 Visit, study staff will complete a final study contact with each mother to confirm her transition and, in particular, confirm her access to non-study ARVs. Mothers will also be asked to report their non-study ARV regimen, their adherence to non-study ARVs, any potential intolerance or side effects associated with their non-study ARVs, and any other problems with accessing or taking their non-study ARVs. This contact should take place within four weeks after the Week 50 Visit and should be documented in each mother’s study chart. [paragraph continues]
27. In Section 6.16, third paragraph, the website for accessing WHO guidelines for newborn step-wise surface examinations is updated. In addition, procedural expectations for assessing infant growth (fifth paragraph) are clarified as follows:

At all visits, additional assessments may be performed at the discretion of the examining clinician. Also at all visits, the measurements listed above should be charted on standard infant growth charts and will be used to determine weight-for-length z-scores, which will be assessed in relation to WHO growth standards; measurements may also be charted on standard infant growth charts.

28. In Section 6.18.1, third paragraph, maternal blood collection priorities are clarified as follows:

In the event that maternal blood collection must be limited, available specimens should be prioritized for use in the following order: (1) HIV-1 RNA, (2) chemistry, (3) hematology, (4) CD4+ cell count, and (5) (1) confirmatory HIV testing (if needed at Screening Visit), (2) HIV-1 RNA, (3) chemistry, (4) hepatitis B surface antigen (at Entry Visit only), (5) hematology, (6) CD4+ cell count, and (7) plasma, cell pellet, and serum storage for purposes other than HIV-1 RNA.

29. In Section 6.18.2, fourth paragraph, expectations for specimen shipping are updated as follows:

Most specimens collected and stored at site laboratories per the Schedule of Evaluations are expected to be requested for centralized testing after all participants have completed follow-up (through Week 50 postpartum). However, an interim shipment is planned when all enrolled mothers have delivered. At this time, all specimens stored for centralized HIV-1 RNA testing will be requested for shipment to the designated testing laboratory. These specimens will then be tested as needed to evaluate outcomes through the delivery time point. Interim shipments may also be required for urine samples stored for evaluation of markers of renal toxicity. Alternative shipping arrangements may be specified by the Protocol Team as needed; detailed shipping instructions will be provided in the LPC.

30. In Sections 7 and 9.5, roles and responsibilities for monitoring participant safety are modified to specify that a Safety Review Group (SRG), rather than the Clinical Management Committee (CMC), will perform routine reviews of participant safety data, as follows:

Section 7

Participant safety will be carefully assessed, monitored, and reported at multiple levels throughout this study. Sections 7.1-7.3 describe safety-related roles, responsibilities, and procedures. The safety monitoring roles of the CMC study-specific Safety Review Group (SRG) and DSMB are briefly referenced in Section 7.1 and described in greater detail in Sections 9.5.2 and 9.5.3.

Section 7.1.2, Clinical Management Committee (CMC)

The following Protocol Team members comprise the CMC: Protocol Co-Chairs, selected Protocol Investigators, Medical Officers, Statisticians, Data Managers, and Clinical Trial Specialists. The CMC will provide guidance as needed to site investigators regarding all aspects of participant management, including but not limited to questions of participant eligibility, management of AEs, and management of antiretroviral regimens. On behalf of the full Protocol Team, the CMC will also monitor participant safety through routine review of study data reports as described in Section 9.5.1.
Section 7.1.3 (added), Safety Review Group
An SRG comprised of the Protocol Medical Officers, Protocol Statisticians, Protocol Data Managers, and other designated individuals with expertise in adult HIV medicine, obstetrics, and pediatrics who are independent of the Protocol Team will monitor participant safety through routine review of study data reports as described in Section 9.5.2.

Section 9.5.1, Monitoring by the Protocol Team

**Participant Safety**

**Routine CMC Safety Data Reviews**

On behalf of the Protocol Team, the CMC will closely monitor participant safety through routine review of safety data reports generated by the SDMC. These reports will provide tabulations of the maternal and infant adverse events specified for entry into eCRFs in Section 7.2. The CMC will review these reports via conference call or other meeting at least monthly. At the time of each review, the DAIDS Medical Officer will also review any EAEs (defined in Section 7.3) reported to the DAIDS Safety Office that are not yet reflected in the data reports. The CMC will continually evaluate the pattern and frequency of reported events and assess for any individual occurrences or trends of concern.

**Section 9.5.2 (added), Monitoring by the SRG**
The SRG will monitor participant safety through routine review of safety data reports generated by the SDMC. These reports will provide tabulations of the maternal and infant adverse events specified for entry into eCRFs in Section 7.2 pooled across the three randomized study arms. The SRG will review these reports via conference call or other meeting at least monthly. At the time of each review, the DAIDS Medical Officer will also review any EAEs reported to the DAIDS Safety Office that are not yet reflected in the data reports. The SRG will continually evaluate the pattern and frequency of reported events and assess for any individual occurrences or trends of concern. If the SRG identifies a potential safety concern, the Protocol Statisticians or Medical Officers will notify the DSMB and request further DSMB review and recommendations; among the recommendations requested will be whether the CMC should be informed of the SRG and/or DSMB review findings.

31. In Section 7.2.1, requirements for entering maternal adverse events into eCRFs are modified to include events involving immune reconstitution inflammatory syndrome, as follows:

**Adverse Events**

The following adverse events — inclusive of abnormal laboratory test results and clinical signs, symptoms, and diagnoses except as specified in the IMPAACT Do Not Report List — will be entered into maternal adverse events eCRFs:

- All grade 3 or higher adverse events
- All grade 2 or higher rashes
- All grade 2 or higher psychiatric events
- All events involving suicidal ideation or attempt
- All suspected or confirmed diagnoses of clinical hepatitis
• All suspected or confirmed diagnoses of immune reconstitution inflammatory syndrome (IRIS)
• All adverse events that lead to any change of ART regimen (i.e., any hold, discontinuation, switch/replacement, dose or frequency modification)
• All serious adverse events (SAEs) as defined in Version 2.0 of the DAIDS EAE Manual

In Section 8.8, guidance related to assessing relation of IRIS events to study drug and reporting IRIS events as expedited adverse events is added, as follows:

As noted in Section 8.1, adverse events assessed as secondary to immune reconstitution should not be considered related to study drug; the rationale for this is that although IRIS is related to ART initiation, assessment of relationship of IRIS to a specific ART regimen is not meaningful for a given event. In addition, the DAIDS EAE Manual specifies that IRIS events should not be reported as EAEs, as IRIS is considered an anticipated event for antiretroviral therapies.

32. In Section 7.3.2, the second paragraph has been added (below Table 5) and the third paragraph has been modified to provide further instructions for expedited adverse event (EAE) reporting for mothers who switch ART regimens, as follows:

For mothers in Arm 1 or Arm 2, the EAE reporting categories listed above will be remain unchanged regardless of ART regimen changes. For mothers in Arm 3 who switch to a DTG-containing or TAF-containing regimen, the EAE reporting category will also be switched to the SAE reporting category, from the date of the switch through study exit.

In addition to the above, the following must also be reported in an expedited manner (i.e., as EAEs) for mothers in Arm 1 or Arm 2 and for mothers in Arm 3 who switch to a DTG-containing or TAF-containing regimen:

• Pregnancy complications that result in medically indicated and/or elective termination of the pregnancy
• Spontaneous abortions and fetal deaths

33. Section 8.7 has been modified to include guidance related to headache and anxiety associated with use of DTG as well as guidance in relation to administration of the Pittsburgh Sleep Quality Index (PSQI), Generalized Anxiety Disorder 7-Item Scale (GAD-7), and Edinburgh Postnatal Depression Scale (EPDS), as follows:

As described in Section 1.8, use of EFV is commonly associated with nervous system symptoms (e.g., dizziness, impaired concentration, somnolence, abnormal dreams, and insomnia) that usually begin on the first or second day of therapy and resolve within 2-4 weeks on therapy. To minimize these possible effects, mothers receiving EFV in this study will be encouraged to take EFV at bedtime; mothers will also be informed of the potential for exacerbation of these symptoms associated with use of alcohol and psychoactive drugs.

DTG is also associated with insomnia, which is generally mild and a short-term tolerability issue. Insomnia, headache, and anxiety have been reported with DTG. Participants who experience insomnia with evening dosing of DTG may have resolution of insomnia after switching to morning dosing (123).
Mothers who experience nervous system symptoms should generally be managed consistent with the guidance provided in Table II.1. For any mothers who experience persistent symptoms that cannot be tolerated, the CMC should be consulted regarding a change of study drug regimen.

Serious psychiatric adverse events, including severe depression and suicidal ideation or attempts, have also been observed with use of EFV (and rarely with DTG). Patients with a history of psychiatric disorder are a highest risk for these events; for this reason, mothers with a history of suicidality or psychiatric illness that requires treatment with psychoactive medication will be excluded from this study.

Mothers who enroll in the study will be assessed for depression through collection of medical history information at each scheduled visit as well as through administration of the Edinburgh Postnatal Depression Scale (EPDS) at Weeks 6 and 50 postpartum. Further information on administering the EPDS, and interpreting scores on this scale, is provided in the study-specific MOP. Participants identified with depression, or with EPDS scores indicating a possibility or probability of postpartum depression or harm to self, will be referred to appropriate mental health services for further evaluation and/or treatment; each study site must establish SOPs for identification and referral of participants requiring mental health services prior to study initiation. The EPDS is not intended to be — and should not be — used to make decisions regarding study drug changes, although responses to the EPDS may prompt further evaluation for depression or other mental health problems. Further guidance on management of depression is provided in Table II.6.

Mothers who enroll in the study will be assessed for sleep disturbances, anxiety, and depression through collection of medical history information at each scheduled visit as well as through administration of the Pittsburgh Sleep Quality Index (PSQI), Generalized Anxiety Disorder 7-Item Scale (GAD-7), and Edinburgh Postnatal Depression Scale (EPDS). Further information on administering these standardized questionnaires is provided in the study-specific MOP.

The PSQI, GAD-7, and EPDS are not intended to be — and should not be — used for diagnostic purposes or to make decisions regarding study drug changes. However, responses to these questionnaires may prompt further evaluation for neuropsychiatric problems. For participants with questionnaire responses indicating possible neuropsychiatric symptoms of concern, a designated study staff member will continue discussion with the participant to determine whether she may require additional support, evaluation, and/or treatment, following site SOPs.

The DAIDS AE Grading Table provides guidance on grading the severity of insomnia, psychiatric disorders (including anxiety and depression) and suicidal ideation or attempt. Study-specific guidance for management of these conditions is provided in Table II.6. As indicated this table, any participant identified with a grade 1 or grade 2 condition accompanied by suicidal ideation, or any grade 3 or 4 condition, should be referred to appropriate mental health services.

34. Section 9 is updated (throughout) to reflect study design and statistical considerations associated with the modified primary and secondary objectives as well as all other protocol modifications. Consistent with current requirements for submitting study results to ClinicalTrials.gov, the outcome measures specified in this section have been categorized as primary, secondary, other, and exploratory.
35. Section 10.2 and the sample informed consent forms in Appendices III and IV are updated to state that other US, local, and international drug regulatory entities may inspect study records.

36. In Appendix II, the third and fourth rows in Table II.3 are updated to clarify references to total versus direct bilirubin test results. Also in Appendix II, the first and third rows in Table II.6 are updated to more clearly provide guidance for grade 1 and 2 maternal psychiatric adverse events with suicidal ideation separate from guidance for events without suicidal ideation.

37. In Appendix III, the sample informed consent form for mother-infant pair study participation is updated to reflect the current study drug Package Inserts and all other applicable protocol modifications, as follows:

About the Study (second paragraph)
You are being asked to join this study with your baby because you are pregnant and have HIV. The study will include about 550 to 640 mothers and babies from Botswana, Brazil, Haiti, India, Malawi, South Africa, Thailand, Uganda, the United States, Tanzania, and Zimbabwe. Each mother and baby will be in the study during pregnancy and for about 1 year after the baby is born.

Item 5 (first paragraph)
The study requires an ultrasound scan of your baby [sites may use locally appropriate terminology to refer to the scan]. The scan uses sound waves to check the size of your baby, which shows how long you have been pregnant. Ultrasound scans are commonly done among pregnant women. If you have already had this type of scan done (outside the study), we may be able to use that scan for the study. If not, we will do the scan as part of the study.

Item 6 (fourth paragraph)
If you do not qualify for the study, or you decide not to join, we will tell you where you can go for ARVs and other care you and your baby may need. [Sites may insert locally appropriate information as needed:] There are programs available for pregnant women with HIV and their babies. You have the option to receive services from these programs as an alternative to being in this study. If you do not join the study, the blood drawn at your first visit will not be kept for later testing (it will be destroyed).

Item 10, (last paragraph under For mothers, we also will)
When your baby is 6 weeks and 12 months of age, we will ask some questions about how you have been feeling (for example, if you have felt happy or sad or scared). Sometimes mothers feel abnormally sad after having their babies. This is called postpartum depression. If the questions show that you have been sadder than normal, we will talk with you about this. We will also tell you about other services outside the study that might help you.

Item 10, (last paragraph under For babies, we also will)
If any test done for the study shows that your baby has HIV, we will ask you to bring your baby to the clinic as soon as possible for another test. **We will collect about 3 mL (less than 1 teaspoon) of blood for HIV testing and for later testing for resistance.** Whether your baby has HIV or not, you and your baby will stay in the study as originally planned. The study cannot provide care and treatment for babies who have HIV, but we will tell you where you can go for the care and treatment your baby may need.
Item 11 (newly added)
11. We will ask questions about how you have been sleeping and feeling.

At some visits, we will ask questions about how well you have been sleeping and how you have been feeling (for example, if you have felt happy or sad or scared). Sometimes mothers feel abnormally sad after having their babies. This is called postpartum depression. If the questions show that you have been sadder than normal, we will talk with you about this. We will also talk with you about problems with sleep or feeling anxious. If you have these types of feelings or problems, we will tell you about other services outside the study that might help you.

Item 12 (formerly item 11) (fourth bullet point)
Draw your blood (up to 12 mL or about 2-3 teaspoons) for tests. The tests will check your HIV viral load. If you changed ARVs, the tests will also check how well your liver and kidneys are working. If your HIV is not controlled, some blood will be saved for later testing for resistance the tests will check for resistance. Some blood will be saved for later testing.

Item 22 (formerly item 21) (third bullet point)
- Build-up of acid in blood, called lactic acidosis, very enlarged liver, fatty liver, or death have been reported. If you have these problems, you might have unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness, dizziness, and shortness of breath. This can be caused by FTC and tenofovir.

Item 23 (formerly item 22) (box for Effects on Your Blood, second bullet point, added)
More acid in the blood that may be related to liver problems

**Modifications Introduced in Protocol Version 1.0 Clarification Memorandum #2**

1. On the protocol cover page, the Investigational New Drug (IND) application number under which the study will be conducted (IND # 133,438) has been added.

2. Section 7.3.3 has been modified to specify use of the current DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, as follows:

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated July 2017 Version 2.0, dated November 2014, will be used in this study. This table is available on the RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables. In addition, the following protocol-specific grading scheme for axillary measured fever will be used in this study:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Temperature Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37.4 to &lt;38.0°C</td>
</tr>
<tr>
<td>2</td>
<td>38.0 to &lt;38.7°C</td>
</tr>
<tr>
<td>3</td>
<td>38.7 to &lt;39.4°C</td>
</tr>
<tr>
<td>4</td>
<td>≥39.4°C</td>
</tr>
</tbody>
</table>

**Note:** The DAIDS AE Grading Table parameter for uninentional weight loss excludes postpartum weight loss. Therefore, maternal weight loss will not be graded in this study.
3. Inclusion criteria 4.1.5 and 4.1.6 and several other protocol sections have been modified to clarify that fetal ultrasound scans performed during the current pregnancy 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 electronic case report forms (eCRFs) for estimation of gestational age.

**Note below inclusion criteria 4.1.5 and 4.1.6**

*Note: For criteria 4.1.5 and 4.1.6, fetal ultrasound is preferred but not required for purposes of eligibility determination. If ultrasound cannot be performed during the study screening period prior to study entry, it must be performed within 14 days after study entry. As further explained in Section 6.1, enrolled participants will not be withdrawn from the study based on ultrasound findings obtained after study entry.*

**Section 6.1, fourth bullet point**

- Fetal ultrasound should be performed if possible during the study screening period to estimate gestational age and assess for multiple gestation and fetal anomalies. Every effort should be made to perform ultrasound during the screening period (prior to study entry). Every effort should be made to perform fetal ultrasound to estimate gestational age and assess for multiple gestation and fetal anomalies prior to study entry. However, if this is not possible, the best available method should be used to perform these assessments for eligibility determination. In these cases, ultrasound must be performed as soon as possible and within 14 days after study entry and the ultrasound findings will subsequently be used in algorithms to calculate gestational age at study entry and gestational age at delivery. If ultrasound is performed during the screening period prior to study entry, results must be considered for purposes of eligibility determination. For example, if ultrasound performed prior to study entry indicates multiple gestation during the screening period, the mother (and her fetuses) should not be enrolled. However, if ultrasound is performed after study entry, enrolled participants will not be withdrawn from the study if the ultrasound identifies an exclusionary condition.

*Note: In the event that fetal ultrasound was performed prior to the study screening period, and a result report meeting all requirements specified in Section 6.13 is available, it is not necessary to perform another scan for study purposes.*
Section 6.1, Clinical row of procedural table, fifth bullet point

- Perform fetal ultrasound if possible (and if not performed prior to the study screening period)

Section 6.2, fifth paragraph

As noted in Section 6.1, fetal ultrasound should be performed if possible during the screening period prior to study entry if possible. (paragraph continues)

Section 6.13

A fetal ultrasound scan is required to permit more accurate calculation of gestational age at entry into the study and gestational age at delivery. Scans should be performed during the study screening period prior to study entry if possible, but may be performed within 14 days after study entry if necessary. When scans are performed prior to study entry, results must be used to estimate gestational age and assess for evidence of multiple gestation and fetal anomalies for purposes of eligibility determination. 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.

Ultrasound scans may be performed at the study site or at off-site facilities. In the event that a scan is performed prior to the study screening period, and a result report meeting all requirements specified below is available, it is not necessary to perform another scan for study purposes.

A result report that minimally documents the following must be obtained for filing in participant study charts and entry into eCRFs; if more than one result report that meets these requirements is available, the earliest available results should be entered into eCRFs for estimation of gestational age:

- Date of scan
- Number of fetuses
- Estimated fetal weight if greater than 20 completed weeks gestation
- Biometry measures for crown-rump length or femur length, abdominal circumference, biparietal diameter, and/or head circumference
  - If less than 14 completed weeks gestation:
    - Crown-rump length
  - If 14 or more completed weeks gestation:
    - Femur length
    - Abdominal circumference
    - Biparietal diameter and/or head circumference

- Calculated ultrasound-based gestational age on the date of the scan or ultrasound-based estimated date of delivery

If any fetal anomalies are identified, these should also be documented in the result report.

Appendix I, table entry for fetal ultrasound during screening prior to or within 14 days after entry
4. In Sections 6.11 and 6.14, data recording requirements for maternal and infant concomitant medications are clarified as follows:

Table 3
Note: eCRFs will also capture whether traditional medications were taken during follow-up.

| Corticosteroids were taken for fetal lung maturity at any time during pregnancy. |

Table 4
Note: eCRFs will also capture whether traditional medications were taken during follow-up.

5. In Section 6.12, data recording requirements for maternal physical examinations are clarified as follows:

All exam findings should be source documented and the following should be entered into eCRFs: height (only at screening exam), weight, blood pressure, and fundal height and fetal heart rate (only at antepartum exams). [paragraph continues]

6. In Section 6.16, required elements of newborn step-wise surface examination components are clarified as follows:

- Newborn step-wise surface examination of:
  - Physical appearance
  - Length
  - Weight
  - Skin
    - Head (including fontanels and circumference)
    - Face (including mouth)
    - Neck
    - Chest
    - Abdomen and anus
    - Hips and genitalia
    - Arms, legs, fingers, and toes
    - Spine
  - Auscultation of chest
  - Neurologic assessment