Letter of Amendment #3 for:

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

Version 2.0, dated 8 December 2017

DAIDS Study ID #30129
IND #133,438

Letter of Amendment Date: 10 June 2020

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Information/Instructions to Study Sites from the Division of AIDS

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

This LoA incorporates the contents of protocol Clarification Memorandum (CM) #2, which was issued on 31 March 2020 to safeguard the health and well-being of IMPAACT 2010 study participants in the context of circulating SARS-CoV-2 and the associated COVID-19 pandemic. Per the study Sponsor, sites were instructed to implement the guidance provided in CM #2 immediately.

Upon obtaining IRB/EC approvals and any other applicable regulatory entity approvals, sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential document files for IMPAACT 2010.

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

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Letter of Amendment Signature Page

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

Signature of Investigator of Record	Date

Name of Investigator of Record
(printed)

Summary of Modifications, Rationale, and Implementation

This LoA incorporates the contents of protocol Clarification Memorandum (CM) #2, which was issued on 31 March 2020 to safeguard the health and well-being of study participants in the context of circulating SARS-CoV-2 and the associated COVID-19 pandemic. CM #2 provided operational flexibility for conducting study visits and procedures when needed to ensure ongoing access to maternal study drug and to prioritize the conduct of clinically and scientifically important maternal and infant evaluations when possible.

Consistent with the instructions provided in CM #2, implementation of this LoA is expected to be time-limited in relation to the COVID-19 pandemic. In consultation with IMPAACT Network leadership and the study Sponsor, the IMPAACT 2010 Protocol Team will determine when, in the future, the specifications of this LoA are no longer applicable. When such a determination is made, study sites will be formally notified and instructed to inform IRBs/ECs and other applicable regulatory entities.

Operational Guidance from Protocol CM #2, dated 31 March 2020

This CM provides operational guidance to study sites from the IMPAACT 2010 Protocol Team. The Protocol Team acknowledges that the extent to which site operations may be disrupted by the COVID-19 pandemic may vary across sites and over time. **All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff.** Site investigators should continue to follow current protocol specifications for communication with the Protocol Team and/or Clinical Management Committee and should contact the Clinical Management Committee (impaact.2010cmc@fstrf.org) with any questions or concerns regarding this CM or management of study participants.

Visit Scheduling

- Sites that anticipate operational disruptions or closures in the near future are advised to conduct study visits early in the allowable visit window. Visits conducted prior to opening of the allowable window would also be preferred to completely missing a visit at a later date.
- Sites that are currently experiencing operational disruptions or closures are advised to conduct study visits late in the allowable visit window. Visits conducted after closing of the allowable window would also be preferred to completely missed visits.
- Effective with the issuance of this CM, the allowable window for conducting maternal and infant Week 50 Visits is broadened to include up to 12 weeks before and up to 24 weeks after the visit target date.

Prioritization of Study Visit Procedures

- Sites with full capacity to conduct study visits in-person at the study clinic should continue to do so in full compliance with the protocol.
- Sites may also conduct study visits — in full or in part — off-site if permitted by applicable government, health authority, and institutional policies. Where this option is permitted, site staff should communicate with maternal participants to determine in advance where and when such visits will take place, with adequate protections for safety, privacy, and confidentiality. Off-site visit procedures should be conducted by site staff who are adequately qualified and trained to conduct the procedures, as determined by the site Investigator of Record (IoR), with attention paid to occupational health, biohazard containment, and specimen and data chain of custody. These staff should also be adequately qualified and trained to immediately assess and/or manage any adverse events or social

impacts that may occur during the visits. If adverse events requiring further evaluation or management are identified during an off-site visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee as needed.

- Sites with limited capacity to conduct in-person study visits should prioritize maternal HIV-1 RNA (viral load) testing and infant diagnostic HIV nucleic acid testing (NAT). If these tests cannot be performed consistent with a site's Protocol Analyte List, the tests may be performed in alternate laboratories using alternate assays (alternate laboratories must adhere to local regulations for clinical laboratory testing).
  - Maternal serum creatinine testing is the next highest priority (following maternal HIV-1 RNA testing and infant NAT), followed by other maternal chemistries and hematology. Specimen collection for storage is of lowest priority.
  - Medical and medication histories may be obtained remotely (e.g., by telephone)
  - Adherence assessment, counseling, and support may be provided remotely.
  - Contraception counseling may be provided remotely. Sites should discuss options for ongoing access to contraception throughout the duration of study participation.
  - Questionnaires may be administered remotely.
  - DXA scans may be skipped/missed.

Study Drug Supply

- Prior to the Week 50 visit, sites are advised to dispense maternal study drug supplies in quantities sufficient for the remainder of the study follow-up period, i.e., through the end of the Week 50 visit window.
- At the Week 50 visit, where feasible, sites are encouraged to provide a supply of non-study ARVs or to implement other post-study access plans to facilitate successful maternal transition to non-study ART and care.
- Where feasible, sites are encouraged to implement study drug delivery options involving outdoor pick-up or drop-off. Where outdoor pick-up or drop-off is not feasible, the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* permit shipment or courier of study drug from the site directly to participants. This method should only be used in the short-term and if permissible per local institutional and IRB/EC policies. Refer to the *Guidelines* for additional details on this method.
- Sites are permitted to utilize rapid urine pregnancy test kits (either performed by study staff or given to and performed by mothers themselves) in the context of these study drug pick-up or drop-off options. If pregnancy testing cannot be performed for any reason, however, study drug supplies should still be provided. Dolutegravir will not be provided to any mother who reports that she is newly pregnant.

Documentation

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT 2010.
- Documentation should be entered in participant study charts in real-time should any of the following occur:
  - Missed visits
  - Out-of-window visits
  - Off-site visits (document the location of the visit)
  - Incomplete or partial visits (document which procedures were performed and which were not)
  - Remote contacts performed in lieu of in-person visits (document method used to complete the contact and which procedures were performed)
  - Any other participant contacts
  - Use of alternate laboratories or alternate laboratory assays
  - Alternate provision of study drug

- In consultation with the Division of AIDS, the IMPAACT Network is developing comprehensive guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures during the COVID-19 pandemic. Similar guidance will be provided for documentation of use of alternate laboratories or alternate laboratory assays. Once this Network-level guidance is available, it will be provided in a separate communication to all sites.