Summary of Changes Included in the Full Protocol Amendment of:

IMPAACT 2008
Phase I/II Multisite, Randomized, Controlled Study of Monoclonal Antibody VRC01 with Combination Antiretroviral Therapy to Promote Clearance of HIV-1-Infected Cells in Infants

The Amended Protocol is Identified as:

Version 2.0, dated 29 May 2017

DAIDS Study ID #20735
IND #133,017

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the IMPAACT 2008 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 site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed and all required approvals of this amendment must be obtained before initiating this study. Likewise, informed consent must be obtained for this study using site-specific informed consent forms that correspond to this amendment.

Upon receiving IRB/EC approval, and approval of any other applicable regulatory entities, study sites must submit a registration packet for protocol Version 2.0 to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for protocol Version 2.0 after the DAIDS PRO verifies that all required registration documents have been received and are complete. This notification must be received prior to study initiation at each site.

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 2008.

Summary and Rationale

The main purpose of this amendment is to respond to comments and recommendations received from the United States Food and Drug Administration (FDA) upon review of protocol Version 1.0. Modifications are incorporated into the protocol as follows:

- The introductory and background sections of the protocol have been updated to incorporate additional clinical experience with the study product — VRC01 — following the issuance of protocol Version 1.0. The risks section of the protocol, sample informed consent form, instructions for safety-related notifications to the Clinical Management Committee (CMC), and requirements for expedited adverse event (EAE) reporting have also been updated to reflect this experience.

- The frequency of evaluation following administration of the study product has been increased. The Day 3 study visit has been eliminated, although a contact at Day 3 is retained, and contacts at Weeks 1, 3, 7, and 11 have been replaced with clinic visits. A clinic visit has been added at Week 20.

- Protocol specifications for management of adverse events have been expanded to provide event-specific guidance for injection site reactions; urticaria and other hypersensitivity reactions; serum sickness; elevated ALT, total bilirubin, and creatinine values; and decreased absolute neutrophil counts.

- An early interim safety analysis has been added. This analysis will be performed when the first five participants assigned to receive VRC01 have completed their Week 3 study visits.

- The study objectives involving biomarkers of HIV persistence have been expanded to include total inducible HIV-1 RNA concentration as measured by the tat/rev induced limiting dilution assay (TILDA).

- Instructions for study product storage and preparation have been updated consistent with the current VRC01 Investigator's Brochure (Version 7.0, dated 3 February 2017), which became available following the issuance of protocol Version 1.0. Instructions for study product administration have been expanded to specify standardized use of specialized infusion sets and to describe expectations for dose volumes, infusion times, and numbers of infusion sites per dose.

- Consistent with current requirements for submitting study results to ClinicalTrials.gov, the study objectives and corresponding study outcomes and planned data analyses have been categorized as primary, secondary, other, and exploratory.

- The protocol team and 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 amended protocol is identified as FINAL Version 2.0, dated 29 May 2017.

Implementation

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

1. In the Schema and Section 2, the study objectives have been categorized as primary, secondary, other, and exploratory, and the objective related to HIV persistence has been updated as follows:

   To assess the effect of VRC01 on ~~key~~ biomarkers of HIV persistence in PBMCs:

   - HIV-1 DNA concentration (at Weeks 24 and 48)
   - HIV-1 RNA concentration (multiply-spliced and unspliced; at Weeks 14, 24, and 48)
   - **Total inducible HIV-1 RNA concentration (at Weeks 24 and 48)**

   In Section 9, the study outcomes and analyses have been categorized as primary, secondary, and other. Corresponding to the updated objective shown above, the outcomes in Section 9.2 and the infant Schedule of Evaluations (SoE) in Appendix I have been expanded to include concentration of inducible multiply-spliced HIV-1 RNA measured by TILDA, and Section 9.6.3 has been updated to described planned analyses of TILDA results.

2. In Section 1.1.2, Characteristics of Viral Reservoirs in Early Treated Infants, the sub-section on measures of the latent reservoir has been updated to further clarify the rationale for use of HIV-1 DNA as a primary measure of the latent reservoir and to provide the rationale for use of TILDA results as an additional measure of the reservoir.

3. In Section 1.1.2, Characteristics of Viral Reservoirs in Early Treated Infants, the sub-section on antiviral effects of bNAbs in human trials has been updated to incorporate additional clinical experience with VRC01.

4. In Section 1.2, VRC-HIVMAB060-00-AB (VRC01), sub-Sections 1.2.5-1.2.13 have been updated to incorporate additional clinical experience with VRC01. In sub-Section 1.2.5, Table 2 has been updated. New references associated with these updates have been incorporated into Section 16.

5. Section 1.3, Rationale, has been updated to further clarify the overall rationale for conducting this study of VRC01, in combination with cART, among perinatally HIV-infected infants.

6. Section 1.3.2, Rationale for Dose Regimen, has been updated to state that the VRC01 regimen selected for this study is based on pharmacokinetic modeling using data from the VRC 601, VRC 602, and IMPAACT P1112 studies and the dose used in adult studies of VRC01 for antiviral activity.

7. Section 1.3.3, Rationale for Study Endpoints—Virologic, has been updated to further describe biomarkers currently available for quantifying HIV-1 persistence and to provide rationale for including TILDA evaluations in the study (consistent with the revised study objectives). Table 3 has been expanded to include an entry for TILDA.

8. In Section 3, Study Design, reference has been added to an interim safety analysis that will be conducted when the first five infants in Arm 1 have completed their Week 3 visits. A description of this analysis has been added to Sections 9.5.1 and 9.5.2 as follows:

   In Section 9.5.1, Monitoring by the Protocol Team, Participant Safety
   In addition to the routine reviews described above, given that the VRC01 dosing regimen specified for this study has not previously been administered to infants, an interim safety analysis will be performed when the first five infants in Arm 1 have completed their Week 3 visits. This analysis will include all adverse events for all infants enrolled in the study at the time of the analysis. The CMC will review these data prior to SMC review; participant accrual will continue pending the SMC's review unless a safety-related trigger for SMC review (see Section 9.5.2) is met.

   In Section 9.5.2, Monitoring by the Study Monitoring Committee (SMC), second paragraph
   The first **SMC review of this study is expected at the time of the interim safety analysis, which will be performed when the first five infants in Arm 1 have completed their Week 3 visits. The first regularly** scheduled SMC review will occur after the first 50% of participants are enrolled or at 12 months after the first site is activated to initiate the study (whichever comes first). R**egular r**eviews will **then** be scheduled annually ~~thereafter and~~**. SMC reviews** may also occur on a more frequent or *ad hoc* basis if any issues or concerns arise, or if requested by the SMC. Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges that may be identified during their reviews.

   In Section 9.5.2, Monitoring by the Study Monitoring Committee (SMC), Participant Safety
   As indicated above, the SMC will review an interim safety analysis when the first five infants in Arm 1 have completed their Week 3 visits. This analysis will include all adverse events for all infants enrolled in the study at the time of the analysis; the SMC will additionally focus on safety-related trigger events (listed below). If trigger 1 or trigger 2 is met, or if other safety-related concerns warranting a change of study design are identified, accrual into the study and administration of study product will be paused.

9. Section 5.2, Study Product Formulation and Storage, has been updated to reflect current specifications of the VRC01 Investigator's Brochure (Version 7.0, dated 3 February 2017).

10. In Section 5.3, Study Product Administration, instructions for administration of VRC01 have been revised to specify standardized use of specialized infusion sets and to describe expectations for dose volumes, infusion times, and numbers of infusion sites per dose. An instruction for management of potential immediate hypersensitivity reactions has been added. The current content of this section is as follows:

    Topical anesthetic preparations (e.g., EMLA) should not be applied prior to VRC01 administration.

    VRC01 will be administered subcutaneously by slow push in the thigh using an RMS High-Flo Subcutaneous Safety Needle Set with a 26-gauge needle. Dose volumes are expected to range from 0.8 to 4.0 mL, corresponding to infant weights ranging from 2 to 10 kg. Refer to the study-specific MOP for weight-based dosing tables and detailed instructions for use of RMS needle sets. All dose volumes are expected to be administered as a single infusion over approximately 5-10 minutes; up to 15 minutes may be required for the largest dose volumes. However, if appropriate for an infant's size, a divided dose may be infused at two sites.

When administering VRC01, the thigh in which concomitant immunizations may have been administered within the preceding two weeks should be avoided, if possible, as should any site where the skin or tissue is irritated. The location of each injection site (left or right thigh) must be documented.

If an immediate hypersensitivity reaction occurs during administration, administration should be stopped consistent with instructions provided in the study-specific MOP.

11. Section 5.4, Study Product Supply, is updated to specify provision of RMS High-Flo Subcutaneous Safety Needle Sets with a 26-gauge needles to study sites through the DAIDS Clinical Research Products Management Center.

12. Section 5.5, Study Product Accountability, is updated to specify that the product lot number associated with each administered dose of VRC01 will be recorded in participant study records and entered into eCRFs.

13. Section 6, Study Visits and Procedures, and the infant SoE in Appendix I have been updated to increase the frequency of evaluation as noted on page 2 of this document. Due to the increased visit frequency, and to ensure compliance with pediatric blood draw guidelines, the timing of some evaluations has been adjusted.

    - In Section 6.3, the Day 3 Visit that was previously specified for infants in Arm 1 has been replaced with a Week 1 Visit for all infants.
    - In Section 6.4, required laboratory evaluations at the Week 2, Week 6, and Week 10 visits have been modified to include the following:
      - HIV-1 RNA (with storage of residual PBMCs if possible) *(Weeks 6 and 10)*
      - Stored plasma and PBMCs for primary, secondary, and other evaluations
    - In Section 6.5, Week 3, Week 7, and Week 11 Visits have been added for all infants.
    - In Section 6.8, a Week 20 visit has been added for all infants.
    - In Sections 6.7, 6.10, and 6.13, cART adherence assessment has been added.
    - In Section 6.13, a complete blood count has been added at Early Discontinuation visits.
    - In Appendix I, the SoE table and footnotes have been updated to reflect all other modifications in Section 6 and to modify blood draw volumes at selected visits.

    In addition, a statement was added to Section 6.12 to specify that Cerebral Spinal Fluid (CSF) Collection Visit procedures should not be performed if residual CSF cannot be retrieved and stored.

14. In Section 6.16, Monitoring for Reactogenicity, procedural requirements have been updated to reflect the replacement of previously-specific telephone contacts with in-clinic visits at Weeks 1, 3, 7, and 11. References to further information on management of reactogenicity events in Section 8 of the protocol have been added. The current content of this section is as follows:

    Reactogenicity outcomes will be source documented and entered into eCRFs as specified in Section 7.2 below. **Refer to Section 8 for further information on management of reactogenicity events.**

Monitoring by Site Clinicians

Site clinicians will monitor infants randomized to Arm 1 for reactogenicity on each day of administration of VRC01, i.e., at Entry and at Weeks 2, 6, and 10:

- Prior to each injection, as part of the physical exam required at the visit, the infant's **skin**, temperature, heart rate, respiration rate, and blood pressure (if possible) will be assessed, and the site of injection will be visually inspected.

- At 15 and 30 minutes (±5 minutes) after each injection, the infant's **skin**, heart rate, and respiration rate will be assessed, and the site of injection will be visually inspected. If these assessments suggest a possible local or systemic reaction, the infant's temperature and blood pressure should be assessed, and a physical examination of relevant body systems and any other clinically indicated procedures should be performed.

- One hour (±15 minutes) after each injection, the infant's **skin**, temperature, heart rate, respiration rate, and blood pressure (if possible) will be assessed. The site of injection will be visually inspected and gently palpated to assess for induration and tenderness. On Day 0, these assessments will also be performed two hours (±15 minutes) after injection. If these assessments suggest a possible local or systemic reaction, a physical examination of relevant body systems and any other clinically indicated procedures should be performed.

- **If any grade 3 or higher local or systemic reaction is identified following any injection, the infant should be observed at the study site for at least two hours after administration of VRC01 (see Section 8).**

Note: If any scheduled dose of VRC01 is missed for any reason, the above-listed monitoring is not required on the date of the scheduled dose.

At all time points, additional assessments may be performed at the discretion of the examining clinician. The findings of all reactogenicity assessments will be source documented and entered into eCRFs. Site clinicians may choose to photograph observed reactions and to share photographs with the CMC for awareness and to assist with evaluation of the reaction; all grade 3 or higher reactions should ideally be photographed. Standard precautions will be followed to ensure that participant privacy and confidentiality are protected when photographs are shared.

Monitoring by Mothers (or Caregivers) ***including +3-Day Contacts***
The mothers (or caregivers) of infants in both arms will be instructed to complete memory aid documents to record infant signs and symptoms for seven days following the Entry and Week 2, 6, and 10 visits (VRC01 administration visits), beginning on the day of each visit. The memory aids will capture mothers' assessments of local injection site reactions (redness, warmth, swelling, tenderness) for infants in Arm 1) and systemic signs and symptoms (temperature, rash, swelling of joints, vomiting, diarrhea, alertness, feeding, sleeping, irritability) for infants in both arms. For infants in Arm 1, if any scheduled dose of VRC01 is missed, monitoring for local injections site reactions is not required, but monitoring for systemic signs and symptoms should still be performed.

Three ~~and seven~~ days after ~~each~~ visit**s at which VRC01 is administered**, mothers (or caregivers) will be contacted by ~~a~~ study nurse or clinician **staff** to report their reactogenicity assessments by telephone~~, with the exception that – for infants in Arm 1 – the Day 3 visit will substitute for the first telephone contact~~. In-person or home visits may also be substituted for ~~other~~ telephone contacts if preferred by study staff or mothers. **Seven days after each visit (i.e., at Weeks 1, 3, 7, and 11), an in-person visit will be conducted.** The allowable window for the three-day ~~telephone~~ contact**s** is -1 to +3 days; the allowable window for the seven-day ~~contact~~ **visits** is ±3 days. During ~~these~~ **the three-day** contacts **and seven-day visits**, ~~the~~ study ~~nurse or clinician~~ **staff** will ask mothers questions that follow the format of the memory aid document, probing as needed to clarify relevant details, and will record reported signs and symptoms on study-specific source documents. Mothers will also be instructed to proactively contact study staff at any time ~~within the seven-day period~~ **between contacts and visits** if any grade 1 or higher signs or symptoms are identified. If ~~any such~~ **grade 1 or higher reactogenicity** signs or symptoms are reported ~~during or between scheduled contacts~~, mothers will be instructed to return to the study clinic with their infants as soon as possible (within 48 hours) for further evaluation.

As specified in Section 7.2, all reactogenicity findings will be entered into eCRFs.

15. In Section 7.3.1, EAE Reporting to DAIDS, websites and contact details for resources related to expedited adverse event (EAE) reporting have been updated for consistency with current DAIDS standards.

16. In Section 7.3.2, EAE Reporting Requirements for this Study, the listing of adverse events required to be reported on an expected basis has been updated to include grade 3 or higher urticarial or other hypersensitivity reactions.

17. In Section 7.3.3, Grading Severity of Events, updates have been incorporated to specify use of a newly issued Version 2.1 of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (dated March 2017).

18. Section 8, Participant Management, has been updated to incorporate several modifications and additions.

    - In Section 8.1, Management of Adverse Events, prior text has been re-organized; requirements for reporting selected adverse events to the CMC have been expanded and re-located from protocol Section 7.1.1 to this section; and guidance has been added with respect to diagnosing serum sickness. Sub-sections have been added for guidance on general adverse event management (Section 8.1.1) and event-specific adverse event management (Section 8.1.2).
    - In Section 8.1.2, event-specific guidance tables have been added for injection site reactions; urticaria or other hypersensitivity reactions; serum sickness; elevated ALT, total bilirubin, and creatinine values; and decreased absolute neutrophil counts.
    - In Section 8.2, prior guidance for deferral of VRC01 administration has been updated to refer to the newly added event-specific guidance in Section 8.1.2
    - In Section 8.3, prior guidance for discontinuation of VRC01 administration has been updated to refer to the newly added event-specific guidance in Section 8.1.2

19. In Section 9.5.2, Monitoring by the Study Monitoring Committee (SMC), updates have been incorporated to clarify that the SMC will be provided with unblinding codes at the time of each review of blinded study data.

20. In Section 13.5, Potential Risks, the description of potential risks based on experience in other clinical studies has been updated consistent with updates incorporated into protocol Sections 1.2, as follows:

    VRC01 has not previously been administered to HIV-infected infants, but has been administered to both HIV-infected and HIV-uninfected adults. It also has been administered to newborn HIV-exposed infants. As indicated in Section 1.2, VRC01 has **generally** been well-tolerated by all study populations to date. Among infants, only ~~one~~ mild **to moderate** local reaction**s** ~~(erythema)~~ following subcutaneous administration of VRC01 ~~has~~ **have** been observed to date, and no other adverse events attributable to VRC01 have been identified. Experience with VRC01 in adults also indicates a **generally** mild risk profile, with few and mild **to moderate** local reactions at the site of administration and mild systemic reactions including malaise, myalgia, fatigue, headache, and nausea observed in some **study** participants. **In addition, mild to severe urticarial reactions have been observed rarely.**

21. In Appendix II, Sample Informed Consent Form for Infant Study Participation:

    - Under About the Study (second paragraph), consistent with modifications of the study site roster, reference to study participants from Thailand has been deleted.
    - Under About the Study, item 8 has been updated consistent with study product administration specifications in protocol Section 5.3.
    - Under About the Study, items 9 and 10 have been updated consistent with the study visit schedule in protocol Section 6 and Appendix I; blood draw volumes also have been updated consistent with Appendix I.
    - Under About the Study, item 11 has been updated to clarify expectations for recording reactogenicity outcomes and to reflect the option of home visits for reporting of reactogenicity outcomes, consistent with protocol Section 6.16.
    - Under About the Study, item 17 (third and fourth paragraphs) has been updated to reflect current experience with VRC01, consistent with protocol Section 1.2.

22. Administrative updates and corrections have been incorporated to reflect the modifications described above and for accuracy, consistency, and clarity throughout the protocol.