

Summary of Changes Included in the Full Protocol Amendment of:

**IMPAACT P1115
Very Early Intensive Treatment of
HIV-Infected Infants to Achieve HIV Remission:
A Phase I/II Proof of Concept Study**

The Amended Protocol is Identified as:

Version 2.0, dated 17 September 2018

DAIDS Study ID #11954

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the IMPAACT P1115 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.

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 protocol Version 1.0, re-consent for continued study participation should be obtained using the site-specific ICFs for protocol Version 2.0 at the next scheduled study visit.

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.

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 document files for IMPAACT P1115.

Summary of Modifications and Rationale

The main purpose of this amendment is to expand the early intensive therapy regimens evaluated in IMPAACT P1115. These regimens will be evaluated among approximately 445 mother-infant pairs expected to be enrolled under protocol Version 2.0

Infants enrolled under protocol Version 1.0 will continue to receive the treatment regimen they initiated under protocol Version 1.0 as they continue follow-up under protocol Version 2.0. Infants enrolled under protocol Version 2.0 will receive one of two treatment regimens added in protocol Version 2.0. The added regimens include an integrase strand inhibitor, raltegravir, in addition to nevirapine and two nonnucleoside reverse transcriptase inhibitors. One of the added regimens also includes VRC01, a broadly neutralizing monoclonal antibody. Pediatric safety and pharmacokinetic data recently became available for raltegravir, leading to approval by the United States Food and Drug Administration (FDA) for treatment of infants weighing at least 2 kg. Infant safety and pharmacokinetic data also recently became available for VRC01. These agents offer the potential for a more potent approach toward rapid control of HIV replication and elimination of HIV-infected cells, which will be evaluated under protocol Version 2.0.

Most sections of the protocol have been revised to incorporate modifications associated with evaluation of the two added treatment regimens. The protocol has also been updated to reflect the first meeting of the expert panel that was specified in protocol Version 1.0 to review the criteria for entry into Step 3 of the study. Step 3 of the study is the step in which antiretroviral therapy is interrupted. The expert panel was convened in September 2017 and provided recommendations leading to the criteria specified in protocol Section 4.4. The panel will continue to be convened as study implementation proceeds, described in protocol Section 3.3.

Updated Schedules of Evaluations have been appended to the protocol for mothers and for infants in Steps 1, 2, 3, and 4. Updated sample informed consent forms have been appended to the protocol for mothers in each cohort and for infants in Step 1, Step 2, and Steps 3 and 4.

Implementation

Protocol modifications are described below, generally in order of appearance in the protocol.

1. The protocol cover page has been updated to provide the investigational new drug (IND) application number to which the protocol will be submitted. The cover page has also been updated to add pharmaceutical support provided by Merck Research Laboratories and the National Institute of Allergy and Infectious Diseases Vaccine Research Center and remove pharmaceutical support provided by AbbVie; corresponding changes have also been made in protocol Section 5 and in the sample informed consent forms in Appendix IV.
2. The protocol team roster has 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. A protocol signature page has been added and the table of contents has been updated to reflect current protocol sections and page numbers.

3. The schema has been revised to reflect a total sample size of 905 mother-infant pairs, 460 enrolled under protocol Version 1.0 and 445 expected to be enrolled under protocol Version 2.0, and the planned duration of follow-up in each of Steps 1, 2, 3, and 4. The description of the study population has been revised consistent with revisions incorporated into protocol Sections 3 and 4 (described below).
4. The schema has also been revised to specify the three early intensive therapy regimens to be evaluated under protocol Version 2.0:
 - Regimen 1L: Two nucleoside reverse transcriptase inhibitors PLUS nevirapine PLUS lopinavir/ritonavir (2 NRTIs + NVP + LPV/r)
 - Regimen 2R: Two nucleoside reverse transcriptase inhibitors PLUS nevirapine PLUS raltegravir (2 NRTIs + NVP + RAL)
 - Regimen 2RV: Two nucleoside reverse transcriptase inhibitors PLUS nevirapine PLUS raltegravir PLUS VRC01 monoclonal antibody (2 NRTIs + NVP + RAL + VRC01)
5. The schema has also been revised to include updated secondary objectives and added exploratory objectives; these same revisions are also incorporated into protocol Section 2. The primary objective of the study has not changed.
6. In Section 1, the background and rationale sections of the protocol have been revised to include scientific advances since protocol Version 1.0 was finalized. Sections 1.6, 1.8, and 1.9 provide rationale for the evaluation of RAL and VRC01 as part of early intensive treatment regimens. Sections 1.12 and 1.13 provide rationale for the added exploratory objectives.
7. Section 3 has been expanded to provide detailed descriptions of the study cohorts, early intensive therapy regimens, and participant accrual plans. Descriptions of the study steps have been revised to specify the following durations of follow-up in each step: Step 1, 12 weeks; Step 2, up to 192 weeks; Step 3, up to five years; Step 4, until five years of age or six months after viral re-suppression on ART, whichever is later. This section is also updated to provide the following information related to the expert panel convened to provide recommendations to the protocol team:

Entry into Step 3 (Treatment Cessation) is not expected to occur before 96 weeks (two years) of study participation. Anticipating that important scientific advances in the fields of HIV remission and reservoirs may occur during this time and thereafter, an expert panel comprised of selected protocol team members and other leaders in the field of HIV remission and cure will be convened periodically to review the criteria for entry into Step 3 and provide recommendations to the protocol team on whether to retain or modify these criteria. The panel was first convened in September 2017 and provided recommendations leading to the criteria shown in Section 4.4. The panel will be re-convened when the first child is determined to have met the Step 3 criteria and will continue to meet periodically as additional scientific advances occur. Any modifications of the Step 3 criteria necessitated by the recommendations of the expert panel will be specified in a protocol amendment, and entry into Step 3 will be deferred pending institutional review board/ethics committee (IRB/EC) review and approval on a site-by-site basis.
8. In Section 4, most eligibility criteria entry into Steps 1 and 2 remain unchanged. However, consistent with currently-approved use of RAL, infants enrolled under protocol Version 2.0 must have been at least 36 weeks gestational age and 2 kg at birth. In addition, for infants enrolled in Cohort 2, requirements for pre-study nevirapine dosing have been revised to reflect standard of care dosing.

9. In Sections 4.4 and 4.5, criteria for entry into Steps 3 and 4 have been revised consistent with expert panel recommendations.
10. In Section 4.7, a listing of concomitant medications that should not be co-administered with RAL has been added.
11. Section 5 has been revised (throughout) to describe the three study treatment regimens.
12. Sections 6.0, 6.1, and 6.2 have been revised to include participant and adverse event management considerations for the added treatment regimens.
13. Section 6.3 has been revised to specify updated participant management plans in each step:
 - Clarifications and modifications of HIV testing requirements to confirm *in utero* HIV infection are provided in Section 6.31 and 6.322; the duration of follow-up in Step 1 is extended to 12 weeks in Section 6.31.
 - Clarifications and modifications related to the management of study treatment regimens and the duration follow-up in Step 2 are provided in Section 6.323.
 - Clarifications and modifications related to evaluation for possible entry into Step 3 are provided in Section 6.324. Step 3 informed consent requirements have been highlighted as follows:

The Step 3 eligibility criteria include obtaining informed consent for treatment cessation from the child's parent/guardian. Prior to entry into Step 3, the site investigator will meet with the child's parent/guardian to discuss the child's current clinical status and laboratory test results and inform them that the child meets protocol criteria to enter Step 3 and stop use of ART. Using materials provided by the protocol team, the investigator will also provide informational updates from the fields of HIV remission, reservoirs, and cure to provide current context for the child's potential entry into Step 3. All parent/guardian questions will be answered and the discussion will be documented in detail in the child's study chart. If the parent/guardian requests additional time to make a decision, this will be accommodated and follow-up discussions will be scheduled accordingly. If the parent/guardian agrees to stop the child's use of ART, written informed consent will be obtained and the child will enter Step 3. If the parent/guardian does not agree to stop the child's use of ART, the child will remain in Step 2 (on ART) through Week 192. If the parent/guardian changes his or her mind while the child is still on study, and the child continues to meet criteria for treatment cessation, the child may enter Step 3.

- Clarifications and modifications related to management of children in Steps 3 and 4 are provided in Sections 6.33 and 6.34, respectively.
- Revisions corresponding to the above-listed sections are incorporated into the Schedules of Evaluations in Appendices I and II. The Schedule of Evaluations for Step 2 is also updated to include urine collection for evaluation of cytomegalovirus evaluation.
- Revisions corresponding to the above-listed sections are also incorporated into the criteria for premature discontinuation from follow-up in Section 6.4.

14. Section 6.36 has been added to describe collection of cerebrospinal fluid for exploratory evaluations. Lumbar puncture will not be performed for this study. However, for any HIV-infected infant who undergoes lumbar puncture for clinical care during follow-up, residual cerebrospinal fluid will ideally be stored for study purposes.
15. Section 6.381 has been revised to focus on pharmacokinetic evaluations for RAL and VRC01.
16. Section 7 has been revised to reflect the addition of RAL and VRC01 to the study treatment regimens.
17. Section 8 has been revised (throughout) to reflect the planned sample size for each cohort and each study treatment regimen. Secondary outcome measures have been updated to correspond with revised secondary objectives. Monitoring plans have been updated to reflect revised participant accrual plans as well as participant safety considerations for each treatment regimen. Analysis plans have also been updated.
18. Section 9 has been revised to focus on clinical pharmacology plans for RAL and VRC01.
19. Section 10 has been revised to reflect the requirement to obtain separate informed consent for entry into Steps 3 and 4. This section has also been expanded to more fully describe considerations related to essential and source documents and access to source data; participant confidentiality; study discontinuation; and post-study access to study agents.
20. Sections 11 and 12 have been updated to reflect current IMPAACT policies and procedures.
21. In Appendices I and II, each Schedule of Evaluations has been revised for clarity and to reflect participant monitoring and management consistent with protocol Sections 3 and 6. Evaluations have been specified as appropriate for the three study treatment regimens and as recommended by the expert panel.
22. In Appendix IV, each sample informed consent form has been updated to reflect all other protocol modifications. For mothers, sample forms are provided for each cohort. For infants, sample forms are provided by regimen for Steps 1 and Step 2, and a separate form is provided for Steps 3 and 4.