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

DAIDS Study ID #11954
IND #133,017

This file contains the current IMPAACT P1115 protocol, which is comprised of the following documents, presented in reverse chronological order:

- Letter of Amendment #2, dated 07 April 2020
- Clarification Memorandum #2, dated 31 March 2020
- Clarification Memorandum #1, dated 15 October 2019
- Letter of Amendment #1, dated 24 June 2019
- Protocol Version 2.0, dated 17 September 2018
Letter of Amendment #2 for:

IMPAACT P1115
Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study
Version 2.0, dated 17 September 2018

DAIDS Study ID #11954
IND #133,017

Letter of Amendment Date: 7 April 2020

Table of Contents
Information/Instructions to Study Sites from the Division of AIDS ................................................. 1
Letter of Amendment Signature Page .................................................................................................. 3
Summary of Modifications and Rationale .......................................................................................... 4
Implementation .................................................................................................................................... 4

Information/Instructions to Study Sites from the Division of AIDS

This Letter of Amendment (LoA) is being issued to safeguard the health and well-being of IMPAACT P1115 study participants in the context of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease (COVID-19) pandemic.

The information contained in this LoA impacts the IMPAACT P1115 study and must be submitted to site institutional review boards and/or ethics committees (IRBs/ECs) and other applicable regulatory entities:

• Sites that are currently following study participants in Step 2 must submit this LoA to their IRBs/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.
• Sites that are not currently following study participants in Step 2 must submit this LoA to their IRBs/ECs and other applicable regulatory entities as soon as possible for their information. Approval is not required by the study Sponsor Site; however, approval should be obtained if required by the IRBs/ECs or other applicable regulatory entities.

At all sites, all IRB/EC and regulatory entity requirements must be followed.

Upon obtaining all required IRB/EC approvals and any other applicable regulatory entity approvals, sites that are currently following study participants in Step 2 should immediately begin implementing this LoA. This LoA extends the duration of follow-up in Step 2. For each participant currently in Step 2, informed consent for extended follow-up should be obtained at the next in-person study visit that can be safely conducted after all required IRB/EC and regulatory entity approvals are obtained, using the site-specific version of the sample informed consent form contained in this LoA.
This LoA also includes the contents of protocol Clarification Memorandum #2, which was issued on 31 March 2020 and provided operational flexibility for conducting study visits and procedures when needed to prioritize continued close communication with participant families and ensuring access to effective antiretroviral therapy for participants in Step 2. Per the study Sponsor, sites were instructed to implement the guidance provided in Clarification Memorandum #2 immediately.

All sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will then 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, corresponding site-specific informed consent form (required only at sites that are currently following participants in Step 2), all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential document files for IMPAACT P1115.
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 Conference 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 and Rationale

The purpose of this LoA is to permit an extended duration of follow-up in Step 2 prior to considering antiretroviral treatment cessation in Step 3. This modification is necessary to safeguard the health and well-being of study participants in the context of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease (COVID-19) pandemic. No participants will enter Step 3 or cease ART until further notice, as defined below. To help ensure continued access to effective antiretroviral therapy and to maintain clinical, immunologic, and virologic monitoring in the best interest of participants, follow-up of participants currently in Step 2 will be extended.

This LoA also incorporates the contents of protocol Clarification Memorandum #2, which provided operational flexibility for conducting study visits and procedures during the COVID-19 pandemic. All sites should continue to 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.

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 P1115 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. The prohibition of entry into Step 3 specified above will remain in effect until this determination is made and sites, IRBs/ECs, and other applicable regulatory entities are notified.

Implementation

A. Extended Duration of Follow-Up in Step 2

No participants currently in Step 2 will enter Step 3 or cease treatment until a determination is made, in consultation with IMPAACT Network leadership and the study Sponsor, that this LoA is no longer applicable and treatment cessation may be considered. To permit deferral of evaluation for entry into Step 3 until such time that this determination is made, the duration of follow-up in Step 2 is extended by up to 96 additional weeks. This extension affects protocol text in the Schema and Sections 1.5, 3.3, 4.4.5, 5.1.2.1, 6.3.2.4, 6.4.1, 8.1, and Appendix II-C. In each of these sections, the maximum duration of follow-up in Step 2 is extended from 192 weeks to 288 weeks. In Step 3 inclusion criterion 4.4.5 and elsewhere, reference to Step 2 Week 192 is replaced with Step 2 Week 288.

For children currently in Step 2, sites should continue to conduct Step 2 visits approximately every 12 weeks. Visits through Step 2 Week 192 should be conducted per protocol Appendix II-C. After Week 192, additional visits should be conducted approximately every 12 weeks (±6 weeks) per the schedule shown on page 5, which mimics the schedule in protocol Appendix II-C.

Informed consent was previously obtained for approximately 192 weeks of follow-up in Step 2. Informed consent for extended follow-up in Step 2 should be obtained using the site-specific version of the sample informed consent form provided on pages 6-8 of this LoA. For each child, this should be done at the next in-person study visit that can be safely conducted after all required IRB/EC approvals and any other applicable regulatory entity approvals of this LoA are obtained.
Extended Follow-Up Visits in Step 2

<table>
<thead>
<tr>
<th></th>
<th>Weeks 204, 228, 252, and 276 (± 6 weeks)</th>
<th>Weeks 216, 240, 264, and 288 (± 6 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History$^1$</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical exam$^2$</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology$^{3,4}$</td>
<td>0.5 mL</td>
<td>0-0.5 mL</td>
</tr>
<tr>
<td>Chemistries$^5$</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>CD4$^4$</td>
<td>1 mL</td>
<td>1 mL</td>
</tr>
<tr>
<td><strong>VIROLOGY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA PCR$^6$</td>
<td>3 mL</td>
<td>3 mL</td>
</tr>
<tr>
<td>HIV-1 antibody$^7$</td>
<td>1 mL</td>
<td>1 mL</td>
</tr>
<tr>
<td>Stored droplet digital HIV DNA PCR$^8$</td>
<td>3 mL</td>
<td>3 mL</td>
</tr>
<tr>
<td>Replication-competent virus and single copy HIV RNA$^9$</td>
<td></td>
<td>9 mL</td>
</tr>
<tr>
<td>Stored plasma and PBMC$^{10}$</td>
<td>2 mL</td>
<td></td>
</tr>
<tr>
<td>Stored virology DBS$^{11}$</td>
<td></td>
<td>0.25 mL</td>
</tr>
<tr>
<td><strong>IMMUNOLOGY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored immune responses$^{12}$</td>
<td>3 mL</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL BLOOD VOLUME</strong></td>
<td>14.5 mL</td>
<td>17.25-17.75 mL</td>
</tr>
</tbody>
</table>
INTRODUCTION
Your child has been taking part in the study named above. This study has 4 steps. Your child is in Step 2. When your child entered Step 2, we told you that your child could stay in Step 2 for up to 4 years. You are now being asked to allow your child to stay in Step 2 for longer than 4 years.

This is a consent form. It gives information about the study. Please read it or have it read to you. Ask any questions you may have. After we discuss the information with you, if you choose to allow your child to stay in Step 2 for longer than 4 years, you will be asked to sign this form. You will be offered a copy to keep.

WHAT DOES YOUR CHILD HAVE TO DO AS PART OF THIS STUDY?
In Step 2 of the study, your child has had regular clinic visits to check on his or her health. We have checked your child’s use of anti-HIV medicines (ARVs) and done laboratory tests. We have been reviewing the test results to see if your child may qualify for Step 3. Step 3 is the step in which children stop taking ARVs.

As of now, your child’s test results show that your child may qualify for Step 3. However, we are making changes in the study that affect when children can enter Step 3. These changes are being made because of the illness caused by the new coronavirus, which is called COVID-19.

We will tell you about the things we are doing here, and that you can do in your home life, to avoid getting COVID-19. To protect your child’s health as much as possible, your child should keep taking ARVs while there is a chance that COVID-19 could be affecting our community. Until we can be sure that chance is very low, children in the study will stay in Step 2. This is why we are asking you to allow your child to stay in Step 2 for longer than originally planned.

While your child stays in Step 2, he or she will keep taking ARVs. Your child will also keep having visits about every 12 weeks. If we need to change the schedule of your child’s visits because of COVID-19, we will contact you to arrange for that. As has been done at other visits in Step 2:

- You will be asked about your child’s health, medicines, and feeding.
- Your child will have a physical examination.
- Your child will have about 2-4 teaspoons (10-20 mL) of blood drawn for safety and HIV-related tests. Tests of the amount of HIV in your child’s blood will be done at each visit.

We will continue to talk with you about your child’s ARVs, any ARV changes that may be needed, and any new instructions for giving ARVs to your child. We will continue to review your child’s test results and give the results to you.
We will tell you when a decision is made in the future to allow children who qualify to enter Step 3. At that time:

- If your child qualifies for Step 3, the study doctor will meet with you to discuss this. The doctor will tell you about your child’s health and latest test results. The doctor will also give you an update on what has been learned outside of this study about controlling HIV and starting and stopping ARVs. Because we expect to be learning new information over time, we want you to have the most up-to-date information. You are welcome to ask questions about this at any time.
- If your child does not qualify for Step 3, or you do not want your child to stop taking ARVs, your child will leave the study. We will tell you about other sources of HIV-related care available to your child at that time.

Other than staying in Step 2 longer, no other parts of the study are changing. The information we gave you when your child entered Step 2 about risks, benefits, your child’s rights as a research participant, and protection of your child’s confidentiality remain in effect. Your previous choices about use of your child’s samples also remain in effect. If you want to review any of this information again, we will take as much time as needed to do that with you.

WHAT OTHER CHOICES DOES YOUR CHILD HAVE?
Taking part in this study is completely voluntary. You may choose to not allow your child to stay in this study. Your choice will not result in any penalty or loss of benefits to which your child is otherwise entitled. Please talk with us about the choices available to your child. Whether or not you allow your child to stay in the study, we will tell you about other sources of HIV-related care available to your child. We will also tell you any new information from this study or other studies that may affect your child’s health and welfare or your willingness to have your child stay in this study.

WHAT HAPPENS IF YOUR CHILD IS INJURED?
If your child is injured as a result of being in this study, your child will be given immediate treatment for the injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form.

WHAT SHOULD YOU DO IF YOU HAVE QUESTIONS OR PROBLEMS?
For questions about this study or a research-related injury, contact:
- name of the investigator or other study staff
- telephone number of above

For questions about your child’s rights as a research participant, contact:
- name or title of person on the IRB/EC or other organization appropriate for the site
- telephone number of above
SIGNATURES
If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to allow your child to stay in Step 2 for longer than 4 years, please sign your name below.

Participant’s Name (print)

Parent or Legal Guardian Name (print) Parent or Legal Guardian Signature Date

Study Staff Conducting Consent Process Name (print) Study Staff Signature Date

Witness Name Witness Signature Date
B. Operational Guidance from Protocol Clarification Memorandum (CM) #2, dated 31 March 2020

This CM provides operational guidance to study sites from the IMPAACT P1115 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.P1115cmc@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 the Step 1 Week 12 visit is broadened to ±6 weeks.
  - The allowable visit windows for the Step 2 Week 132, Week 144, Week 168, and Week 180 visits are broadened to ±6 weeks.
  - The allowable window for the Step 2 Week 192 visit is broadened to -6 to +24 weeks.

**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 visits should prioritize specimen collection and laboratory testing consistent with current protocol specifications; HIV-1 RNA (viral load) testing should be given highest priority. At sites where specimen collection and processing can be performed per the Laboratory Processing Chart, but HIV-1 RNA testing cannot be performed in real time, sites may collect, process, and store specimens for later testing.
- For sites with no capacity to conduct in-person visits, medical and medication history information may be collected remotely; antiretroviral (ARV) adherence counseling and support may also be provided remotely.
**Study Drug Supply for Children in Step 2**

- Sites are advised to maintain frequent communication with participant families (e.g., by telephone) to inquire about each participant’s health, use of ARVs, and ARV supplies.
- Study visits are scheduled to occur approximately every three months. To avoid gaps in ARV coverage, sites are advised to dispense ARV supplies in quantities sufficient for at least three and up to six months. ARV supplies should be dispensed regardless of whether other study visit procedures can be performed.
- 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.

**Documentation**

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT P1115.
- 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
  - Non-standard 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. Once this Network-level guidance is available, it will be provided in a separate communication to all sites.
Clarification Memorandum #2 for:

IMPAACT P1115
Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study
Version 2.0, dated 17 September 2018

DAIDS Study ID # 11954
IND #133,017

Clarification Memorandum Date: 31 March 2020

Summary of Clarifications

This Clarification Memorandum (CM) is being issued to safeguard the health and well-being of IMPAACT P1115 study participants in the context of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease (COVID-19) pandemic.

As the study Sponsor, the Division of AIDS (DAIDS) has determined that this CM should be implemented immediately upon issuance. Consistent with United States Food and Drug Administration guidance, institutional review board/ethics committee (IRB/EC) approval of this CM is not required by the Division of AIDS prior to implementation. However, given the context of the COVID-19 pandemic and the importance of the guidance provided in this CM, sites should submit this CM to IRBs/ECs for their information or, if required by the IRBs/ECs, for their review and approval.

The purpose of this CM is to provide operational flexibility for conducting study visits and procedures when needed to prioritize continued close communication with participant families and ensuring access to effective antiretroviral therapy for children in Step 2 of the study.

Implementation of this CM 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 P1115 Protocol Team will determine when, in the future, the guidance provided in this CM is no longer applicable. When such a determination is made, study sites will be formally notified and instructed to inform their IRBs/ECs.

Please file this CM and any applicable IRB/EC correspondence in your essential document files for IMPAACT P1115.
Implementation

This CM provides operational guidance to study sites from the IMPAACT P1115 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 (impaaact.P1115cmc@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 the Step 1 Week 12 visit is broadened to ±6 weeks.
  - The allowable visit windows for the Step 2 Week 132, Week 144, Week 168, and Week 180 visits are broadened to ±6 weeks.
  - The allowable window for the Step 2 Week 192 visit is broadened to -6 to +24 weeks.

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 visits should prioritize specimen collection and laboratory testing consistent with current protocol specifications; HIV-1 RNA (viral load) testing should be given highest priority. At sites where specimen collection and processing can be performed per the Laboratory Processing Chart, but HIV-1 RNA testing cannot be performed in real time, sites may collect, process, and store specimens for later testing.
- For sites with no capacity to conduct in-person visits, medical and medication history information may be collected remotely; antiretroviral (ARV) adherence counseling and support may also be provided remotely.
Study Drug Supply for Children in Step 2

- Sites are advised to maintain frequent communication with participant families (e.g., by telephone) to inquire about each participant’s health, use of ARVs, and ARV supplies.

- Study visits are scheduled to occur approximately every three months. To avoid gaps in ARV coverage, sites are advised to dispense ARV supplies in quantities sufficient for at least three and up to six months. ARV supplies should be dispensed regardless of whether other study visit procedures can be performed.

- 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.

Documentation

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT P1115.

- 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
  - Non-standard 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. Once this Network-level guidance is available, it will be provided in a separate communication to all sites.
Clarification Memorandum #1 for:

IMPAACT P1115
Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study Version 2.0, dated 17 September 2018

DAIDS Study ID # 11954
IND #133,017

Date: 15 October 2019

---

Summary of Clarifications

This Clarification Memorandum serves to correct minor errors or inconsistencies in protocol wording.

Implementation

Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation; however, sites may submit it to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation. The clarifications included in this memorandum, shown below using strikethrough for deletions and bolding for additions, will be incorporated into the next full protocol amendment.

1. In Section 5.1.2.2, Step 2 Regimens, Regimen 2R, Cohort 2 infants 5-10 days of age at entry into Step 2:
   - Cohort 2 infants 5-10 days of age at entry into Step 2:
     - 3 mg/kg orally twice daily from the Step 2 Week 1 Entry visit until the Step 2 Week 4 visit (schedule the Step 2 Week 4 visit as close to 28 days of age as possible)
     - 6 mg/kg orally twice daily starting at the Step 2 Week 4 visit

2. In Appendix II-A, Infant Schedule of Evaluations, Step 1, footnote 9:

   At Week 1, plasma aliquots for RAL and VRC01 concentrations will be obtained from the 2.5 mL of blood collected for plasma and PBMC storage.

3. In Appendix II-B, Infant Schedule of Evaluations, Step 2: Entry through Week 9, Total Blood Draw Volume for Step 2 Entry Visit:

   13.5-15.5 10.5 mL
4. In Appendix II-B, Infant Schedule of Evaluations, Step 2: Entry through Week 9, footnote 6, second bullet point:

- For infants receiving Regimen 2R or 2RV: AST, ALT, ALP, and creatinine at all indicated time points; total bilirubin only at Entry and Week 2 Week 1
Letter of Amendment #1 for:

IMPAACT P1115
Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission:
A Phase I/II Proof of Concept Study
Version 2.0, dated 17 September 2018

DAIDS Study ID # 11954
IND #133,017

Letter of Amendment Date: 24 June 2019

Table of Contents

Information/Instructions to Study Sites from the Division of AIDS ..................................................... 1
Letter of Amendment Signature Page........................................................................................................ 2
Summary of Modifications and Rationale .................................................................................................. 3
Implementation............................................................................................................................................. 3

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT P1115 study, including one of the study informed consent forms, 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 LoA. Unless otherwise specified by site IRBs/ECs or other regulatory entities, no re-consenting for mothers or infants enrolled in the study prior to approval of this LoA is required after approval of this LoA. However, for any infants who qualify for Step 3 of the study, informed consent for Steps 3 and 4 must be obtained using the updated Step 3 and 4 informed consent form corresponding to this LoA. No infants may enter Step 3 prior to review and approval of this LoA and corresponding informed consent form.

All sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will then 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, corresponding site-specific informed consent form for Steps 3 and 4, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential document files for IMPAACT P1115. If the IMPAACT P1115 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.
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 Conference 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 and Rationale

The purpose of this LoA is to:

- Incorporate recommendations from the United States (US) Food and Drug Administration (FDA) into the inclusion criteria for Step 4, Treatment Re-Initiation. Protocol Version 2.0 specified virologic criteria for entry into Step 4. This LoA adds clinical and immunologic criteria for entry into Step 4. This LoA also updates the sample informed consent form for Steps 3 and 4 to reflect the additional Step 4 inclusion criteria.

- Incorporate recommendations from the US FDA into the guidelines for Study Monitoring Committee (SMC) reviews. This LoA increases the frequency of SMC reviews for safety and for treatment cessation.

- Update the expedited adverse event (EAE) reporting period for Step 1. Protocol Version 2.0 specified EAE reporting at the Serious Adverse Event Reporting Category through the Step 1 Week 4 visit. This LoA extends this reporting period to the entire duration of follow-up in Step 1 (i.e., through the Step 1 Week 12 visit).

- Update the Protocol Team roster, update references to DAIDS Regulatory Support Center (RSC) web pages, and incorporate other minor clarifications into the protocol.

Implementation

Modifications of protocol text are shown in four sections (A-D) below, generally in order of appearance in the protocol within each section, using strikethrough for deletions and bold type for additions where applicable.

A. Inclusion Criteria for Step 4

1. In the Schema, Study Design, Step 4:

   Children who experience viral rebound in Step 3 or meet other Step 4 inclusion criteria will enter Step 4, re-start re-initiate ART, and be closely monitored for viral re-suppression on ART until five years of age or six months after re-suppression, whichever is later.

2. In Section 3.3, Study Steps, Step 4: Treatment Re-Initiation

   Children who experience viral rebound in Step 3 or meet other Step 4 inclusion criteria will enter Step 4 and re-start re-initiate ART. Children in Step 4 will undergo frequent HIV RNA testing to monitor their response to ART re-initiation, until five years of age or six months after viral re-suppression on ART, whichever is later.

3. In Section 4.5, Infant Inclusion Criteria for Step 4, Treatment Re-Initiation

   4.5.1 Must have been enrolled in Step 3.
4.5.2 Must have met at least one of the following:

4.5.2.1 Plasma HIV RNA ≥ LOD based on standard quantitative testing performed at the local CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory after ART cessation (see Section 6.3.2 for procedural guidance related to this criterion)

4.5.2.2 Confirmed CD4 cell percentage < 25% or CD4 cell absolute count < the lower limit of normal for age

4.5.2.3 Confirmed or suspected diagnosis of a new WHO Clinical Stage 3 or 4 condition

4.5.2.4 Confirmed or suspected diagnosis of acute retroviral syndrome

4.5.2.5 Otherwise assessed by the site investigator or designee, in consultation with the CMC, as having an indication to re-initiate treatment

Note: Regardless of HIV RNA test results any of the above, any child enrolled in Step 3 may re-initiate ART at the request of his or her parent or guardian; any such child is eligible for inclusion in Step 4.

4. In Section 5.1.4, Step 4 Regimens

Children who enter Step 4 will re-initiate the same ART regimen they received in Step 2 prior to ART cessation upon entry into Step 3.

5. In Section 6.3.3, Treatment Cessation (Step 3)

See APPENDIX II-D.

Upon entry into Step 3, ART will be stopped and the child will be monitored with HIV RNA testing at Weeks 1, 2, 3, 4, 6, and 8, and every four weeks thereafter. To minimize turnaround time, testing will first be performed using an on-demand assay. If this testing yields a positive result, an additional specimen will be collected as soon as possible and within 72 hours for a standard quantitative HIV RNA assay performed at the local CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory. The standard quantitative HIV RNA assay should be performed such that results are available as soon as possible and within 96 hours of specimen collection (any residual samples should be stored for additional testing if needed). Clinical management will be based on the results of standard quantitative HIV RNA assays in consultation with the CMC; the CMC should be informed as soon as possible and within two business days of any positive on-demand assay result and subsequently informed of the standard assay result. Children who maintain HIV RNA < LOD will remain in Step 3 and will have additional testing for evidence of HIV persistence. Children with HIV RNA ≥ LOD will enter Step 4 and re-initiate ART.

The parents or guardians of children in Step 3 will be counseled on the potential symptoms of acute retroviral syndrome and opportunistic infections and instructed to contact study staff should such symptoms occur. Children who develop any indication to re-initiate ART, per the Step 4 inclusion criteria in Section 4.5, will enter Step 4 and re-initiate ART.
6. In Section 6.3.4, ART Re-Initiation (Step 4)

See APPENDIX II-E.

Children will re-initiate ART at entry into Step 4 and be monitored with plasma HIV RNA testing every two weeks through Step 2 Week 12, then every 12 weeks thereafter. The parents or guardians of children in Step 4 will be counseled on the potential symptoms of acute retroviral syndrome and instructed to contact study staff should such symptoms occur. Children whose HIV RNA is not re-suppressed to < LOD by Step 4 Week 12 will have genotypic resistance testing performed if the RNA level is > 1000 copies/mL at the previous visit; if resistance is identified, the ART regimen may be changed in consultation with the CMC. Children will continue to be followed in Step 4 through five years of age or until six months after viral re-suppression on ART, whichever is later.

7. In Section 6.3.5, Management of Infants Co-infected with Tuberculosis

If a child on study ART develops tuberculosis, the site investigator may change the ART regimen, with approval and input from the CMC, to allow co-administration of rifampin anti-tuberculosis therapy. The child will remain on study and, if in Step 2, will be eligible for treatment cessation as long as the criteria in Section 4.4 are met and tuberculosis treatment is successfully completed. Children who develop tuberculosis while in Step 3 will have met inclusion criteria for Step 4 and will re-initiate ART in that step; selection of an appropriate ART regimen to avoid drug interactions with anti-tuberculosis therapy will be made with approval and input from the CMC.

8. In Appendix IV-E, Sample Informed Consent Form for Steps 3 and 4, WHAT DOES YOUR CHILD HAVE TO DO AS PART OF THIS STUDY, Step 3 Visits, last paragraph:

For as long as HIV is not detected in your child’s blood, your child will remain in Step 3, not taking ARVs. If HIV is detected in your child’s blood on two tests, your child will start taking ARVs again. Your child will also start taking ARVs again if his or her CD4 cell count drops below normal or if he or she develops certain health problems. This is done in Step 4 of the study. Step 4 will be explained to you and you will be asked to sign another consent form for that step.

9. In Appendix IV-E, Sample Informed Consent Form for Steps 3 and 4, WHAT ARE THE RISKS OF THE STUDY, second paragraph:

For children who stop taking ARVs, the amount of HIV in the blood may rise to detectable levels. This could cause other problems. For example, your child could become sick with fever, body aches, tiredness, or weight loss. Please contact the study staff if your child has these kinds of problems. A rise in the amount of HIV in the blood could also lead to HIV becoming resistant to ARVs. To avoid this, tests will be done frequently to check for HIV in the blood, and ARVs will be started again if HIV becomes detectable. It is important for your child to come for clinic visits as scheduled for these tests. ARVs will also be started again if your child’s immune system shows signs of weakening.
B. Guidelines for Triggering SMC Reviews

1. In Section 8.5.3.2, Guidelines for Triggering a Safety Review for HIV-Infected Infants

HIV-infected infants: An SMC review for safety will be triggered if two of any of the following occur among infants receiving a given regimen (i.e., Regimen 1L, 2R, or 2RV):

a) life-threatening event assessed as possibly, probably or definitely related to an ARV other than an NRTI OR
b) life-threatening event assessed as possibly, probably or definitely related to VRC01 OR
c) permanent discontinuation of an ARV other than an NRTI for toxicity assessed as possibly, probably, or definitely related to that ARV OR
d) permanent discontinuation of VRC01 for toxicity assessed as possibly, probably, or definitely related to VRC01

If any of the above-listed triggers for HIV-infected infants are met based on the occurrence of two non-hematologic events (among infants receiving a given regimen), a non-hematologic event in an infant receiving regimen 2R or 2RV, enrollment into the study will be paused pending the outcome of the SMC review. Otherwise, the CMC will determine whether to suspend or continue accrual pending the outcome of the SMC review.

Note: Under protocol Version 1.0, the SMC chose to review hematological triggering events for HIV-infected infants on a routine periodic basis rather than ad hoc as events occurred. The same approach may be taken under protocol Version 2.0, if requested by the SMC.

After a safety trigger for HIV-infected infants has been met, and the required SMC review has taken place, the threshold for future triggers will be reset (i.e., the two events that triggered a safety review will not be re-counted as triggers toward future reviews).

An SMC review will also be triggered based on the proportion of HIV-infected infants experiencing the above-listed events. A review will be triggered if, after 30 HIV-infected have been enrolled:

- This proportion is ≥ 0.20 for non-hematologic events.
- This proportion is ≥ 0.30 for hematologic events.

2. In Section 8.5.3.3, Guideline for Triggering a Review of ART Cessation due to Viral Rebound, second paragraph (added)

The SMC will be informed of each case of confirmed viral rebound within 1-2 weeks after identification and will be convened to review aggregate data after every two cases of confirmed viral rebound. The SMC will also be convened if five cases of confirmed viral rebound occur within the first four weeks of ART cessation, counted separately among children who received regimen 1L and children who received regimen 2R or 2RV; at the time of this review (if triggered), the SMC will provide recommendations regarding continued entry into Step 3. Unless otherwise specified by the SMC at the time of these reviews, enrollment into the study and entry into Step 3 will not be suspended pending recommendations from the SMC.
C. EAE Reporting Period for Step 1

1. In Section 7.4, EAE Reporting Period, first bullet point

The EAE reporting period at the SAE Reporting Category for this study encompasses the time when an infant may be receiving the investigational dose of NVP, combination therapy with four ARVs, and/or VRC01.

- In Step 1, this is operationalized as the period from Step 1 Entry through the Week 4 Week 12 visit.
- In Step 2, this is operationalized as the period from Step 2 Entry through the Week 36 visit.

This reporting period also applies to the other medically significant events for which expedited reporting is required (as listed in Section 7.2).

D. Protocol Team Roster Updates, RSC web page updates, and Other Minor Protocol Clarifications and Corrections

1. In the Protocol Team Roster, a Community Advisory Board Representative is added and contact details are updated for the Laboratory Center Specialist:

Nagaawa Jaliaah  
Baylor-Uganda CAB and IMPAACT CAB  
Baylor College of Medicine Children Foundation  
Block 5 Mulago  
PO Box 72052  
Phone: 256-782-292-819  
Kampala, Uganda  
Email: jaaliahnagawa@gmail.com

Diane Costello, BS  
University of California at Los Angeles  
MacDonald Research Laboratory  
675 Charles E Young Drive South  
MRL 4-629  
11075 Santa Monica Boulevard, Suite #200  
Los Angeles, CA 90095  
Phone: 703-862-0820  
Email: dcostello@impaactlabcenter.org  
Email: dcostello@milabcentral.org

2. In protocol Sections 4.8, 7.1, and 7.3 references to resources available from the DAIDS RSC are updated to reflect current RSC web pages, as follows:

Resources related to protocol registration can be accessed at  
https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration

Resources related to EAE reporting can be accessed at  
Resources specific to paper EAE reporting can be accessed at
https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting

Resources related to grading the severity of adverse events can be accessed at
https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables

3. In protocol Section 6.2.5.1, expectations for follow-up of local and systemic reactions are clarified as follows:

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 recorded on CRFs. 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. Infants with local or systemic reactions observed on the day of VRC01 administration will receive standard follow-up care for the reactions; all such reactions will be followed to resolution or stabilization. See also Sections 6.2.6 and 6.2.7 for management of injection site reactions, urticaria, and other hypersensitivity reactions.

4. In Appendices II-A through II-E, references to the “do not record list” are removed from all of the infant Schedule of Evaluation footnotes (this list is not applicable with the case report forms currently in use for recording adverse events in this study).

5. In Appendix II-B, all evaluations indicated in the Step 2 Schedule of Evaluations for RAL and VRC01 (on pages 94 and 95) are clarified as assays performed for STUDY AGENT CONCENTRATIONS.

6. In Appendices II-C and II-D, evaluations indicated under IMMUNOLOGY as “stored responses” (on pages 98 and 102) are clarified as specimens stored for assays of immune responses.

7. In Appendix II-D, Step 3 Schedule of Evaluations, footnote 5 is clarified to indicate that “a positive result” refers to any detectable HIV RNA, as follows:

At Entry, perform a standard quantitative HIV RNA assay at a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory. After Entry, perform on-demand assays with diluted plasma following the laboratory’s validated dilution plan. Refer to the LPC for assay and dilution requirements. If an on-demand assay yields a positive result (any detectable HIV RNA), collect an additional 3 mL of blood as soon as possible and within 72 hours to perform a standard quantitative HIV RNA assay with undiluted plasma at a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory; the standard quantitative HIV RNA assay should be performed as soon as possible and within 96 hours of specimen collection. Store all residual samples.
IMPAACT P1115

VERY EARLY INTENSIVE TREATMENT OF HIV-INFECTED INFANTS TO ACHIEVE HIV REMISSION: A PHASE I/II PROOF OF CONCEPT STUDY

A Multi-Center Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Sponsored by:
The National Institute of Allergy and Infectious Diseases (NIAID) and
*Eunice Kennedy Shriver*
National Institute of Child Health and Human Development (NICHD)

Pharmaceutical Support Provided by:
Merck Research Laboratories
National Institute of Allergy and Infectious Diseases Vaccine Research Center

DAIDS Study ID #11954
IND # 133,017

IMPAACT HIV Cure Scientific Committee Chair: Deborah Persaud, M.D.

Protocol Co-Chairs: Yvonne Bryson, M.D.
Ellen Chadwick, M.D.

Protocol Vice Chair: Mark Cotton, M.Med, FCPaed

NIAID Medical Officer: Patrick Jean-Philippe, M.D.

NICHD Medical Officer: Rohan Hazra, M.D.

Clinical Trials Specialists: Anne Coletti, M.S.
Charlotte Perlowski, M.S.P.H.

FINAL Version 2.0
17 September 2018
# TABLE OF CONTENTS

1.0 INTRODUCTION ........................................................................................................... 15  
  1.1 Background and Rationale ......................................................................................... 15  
  1.2 Treatment Cessation to Assess HIV Remission ...................................................... 18  
  1.3 Planned Treatment Interruption in HIV-Infected Children and Adults Treated during Chronic HIV Infection ................................................................. 18  
  1.4 Planned Treatment Interruption After Acute Infection ........................................... 19  
  1.5 Timing of Treatment Cessation ................................................................................ 20  
  1.6 Rationale for Enhancing Antiviral Options for Very Early Treatment of Perinatal HIV Infection ........................................................................................................ 21  
  1.7 Rationale for Nevirapine and Lopinavir/Ritonavir Dosing ........................................ 23  
  1.8 Rationale for Raltegravir Use in Children ................................................................. 23  
  1.9 Rationale for VRC-HIVMAB060-00-AB (VRC01) Dosing ....................................... 25  
  1.10 Rationale for Formula and Breastfeeding Cohorts and Focus on in utero HIV-infected Infants .......................................................................................................... 27  
  1.11 Rationale for Enrolling HIV-Infected Infants Started on ART within 48 Hours of Birth in a Clinical Setting ................................................................................. 28  
  1.12 Rationale for Studying Congenital Cytomegalovirus (cCMV) .............................. 28  
  1.13 Rationale for Evaluation of HIV Reservoirs in the Central Nervous System (CNS) ................................................................................................................ 29  
2.0 STUDY OBJECTIVES ................................................................................................... 29  
  2.1 Primary Objective ..................................................................................................... 29  
  2.2 Secondary Objectives ............................................................................................... 29  
  2.3 Exploratory Objectives ............................................................................................. 30  
3.0 STUDY DESIGN .......................................................................................................... 30  
  3.1 Study Regimens ........................................................................................................ 30  
  3.2 Study Cohorts ........................................................................................................... 31  
  3.3 Study Steps ............................................................................................................... 32  
4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS ........................................... 33  
  4.1 Maternal Inclusion Criteria ...................................................................................... 33  
  4.2 Infant Inclusion Criteria, Step 1, Evaluation and Initial Treatment of High-Risk Infants ............................................................................................................ 34  
  4.3 Infant Inclusion Criteria, Step 2, Management of Infants with Confirmed in utero HIV Infection ................................................................................................... 35  
  4.4 Infant Inclusion Criteria, Step 3, Treatment Cessation ............................................ 36  
  4.5 Infant Inclusion Criteria, Step 4, Treatment Re-Initiation ......................................... 37  

IMPAACT P1115
FINAL Version 2.0
Page 2 of 169
17 September 2018
4.6 Infant Exclusion Criteria, Step 1 and Step 2 ................................................................. 37
4.7 Concomitant Medications Requiring Pre-Approval .................................................. 37
4.8 Enrollment Procedures ............................................................................................... 38
4.9 Co-enrollment Procedures ......................................................................................... 39

5.0 STUDY TREATMENT ................................................................................................. 39

6.0 PARTICIPANT MANAGEMENT ................................................................................. 48
   6.1 General Toxicity Management Guidelines ................................................................ 49
   6.2 Special Toxicity Management Guidelines .................................................................. 51
   6.3 Participant Management Plan .................................................................................. 62
   6.4 Premature Discontinuation from Study Follow-up .................................................. 66

7.0 EXPEDITED ADVERSE EVENT (EAE) REPORTING ............................................. 67
   7.1 EAE Reporting to DAIDS ....................................................................................... 67
   7.2 EAE Reporting Requirements for this Study .......................................................... 68
   7.3 Grading Severity of Events ...................................................................................... 68
   7.4 EAE Reporting Period ............................................................................................. 69

8.0 STATISTICAL CONSIDERATIONS .......................................................................... 69
   8.1 General Design ......................................................................................................... 69
   8.2 Outcome Measures .................................................................................................. 71
   8.3 Randomization and Stratification .............................................................................. 71
   8.4 Sample Size and Accrual .......................................................................................... 72
   8.5 Monitoring ............................................................................................................... 78
   8.6 Analyses ................................................................................................................... 81

9.0 CLINICAL PHARMACOLOGY PLAN ........................................................................ 82
   9.1 Pharmacology Objectives ....................................................................................... 82
   9.2 Primary and Secondary Data ................................................................................... 82
   9.3 Laboratory Analysis and Reporting ......................................................................... 83
   9.4 Study Design, Modeling, and Data Analysis ............................................................ 83

10.0 HUMAN SUBJECTS ................................................................................................. 84
    10.1 Institutional Review Board/Ethics Committee and Informed Consent .................... 84
    10.2 Essential and Source Documents and Access to Source Data ............................... 84
    10.3 Participant Confidentiality .................................................................................... 85
    10.4 Study Discontinuation ........................................................................................... 85
    10.5 Post-Study Access to Study Agents ....................................................................... 86

11.0 PUBLICATION OF RESEARCH FINDINGS ......................................................... 86

12.0 BIOHAZARD CONTAINMENT .............................................................................. 86

13.0 REFERENCES .......................................................................................................... 87

APPENDIX I ................................................................................................................... 91
APPENDIX II-A .............................................................................................................. 92
APPENDIX II-B .............................................................................................................. 94
APPENDIX II-C .............................................................................................................. 98
APPENDIX II-D .............................................................................................................. 101
LIST OF TABLES

Table 1: Sample size goals for HIV-infected infants ................................................................. 72
Table 2: Probability of observing 20-40 in utero HIV-infected neonates with various sample sizes assuming a binomial distribution ......................................................................................................................... 74
Table 3: Probability of observing no event (e.g., HIV remission or meeting ART cessation criteria) and of observing at least 1-20 events with sample sizes of 10-40 ......................................................................................................................... 75
Table 4: 95% confidence interval (CI) for the probability of an event (e.g., HIV remission) with sample sizes (and event numbers) of 10-40 ......................................................................................................................... 77
Table 5: Probability of meeting the guidelines to pause ART cessation for an ad hoc SMC review under a range of hypothetical true rebound probabilities ......................................................................................................................... 81
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 Conference 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
IMPAACT P1115
VERY EARLY INTENSIVE TREATMENT OF HIV-INFECTED INFANTS TO ACHIEVE HIV REMISSION: A PHASE I/II PROOF OF CONCEPT STUDY

PROTOCOL TEAM ROSTER

Refer to the study-specific Manual of Procedures (MOP) for detailed guidance on managing study-related questions and other communications with the Protocol Team.

Protocol Co-Chairs
Yvonne Bryson, M.D.
Global Pediatric Infectious Diseases
David Geffen School of Medicine at UCLA
10833 Le Conte Ave. MDCC 22-442
Los Angeles, CA 90095-1752
Phone: 310-825-5235
E-mail: ybryson@mednet.ucla.edu

Ellen Chadwick, M.D.
Northwestern University Feinberg School of Medicine, Division of Infectious Diseases
Ann & Robert H. Lurie Children’s Hospital of Chicago
225 E. Chicago Ave,
Chicago, IL 60611
Phone: 312-227-4080
E-mail: egchadwick@luriechildrens.org

Protocol Vice Chair
Mark Cotton, M.Med, FCPaed (SA), DCH (SA), DTM&H, PhD
Department Paediatrics & Child Health
Faculty of Health Science
FAMCRU, Stellenbosch University
P.O. Box 19063
Tygerberg, 7505
South Africa
Phone: 27 21 938 4219
E-mail: mcot@sun.ac.za

Division of AIDS Medical Officer
Patrick Jean-Philippe, M.D.
Maternal Adolescent Pediatric Research Branch
DAIDS/NIAID/NIH
5601 Fishers Lane, Room 8B49
MSC 9831
Rockville, MD 20852-9831
Phone: 240-292-4790
Email: jeanphilippep@niaid.nih.gov

NICHD Medical Officer
Rohan Hazra, M.D.
Eunice Kennedy Shriver National Institute of Child Health and Human Development
6710B Rockledge Drive, Room 2113
MSC 7002
Bethesda, MD 20817
Phone: 301-435-6868
Email: hazrar@mail.nih.gov

Protocol Data Managers
Bonnie Zimmer, B.S.
Frontier Science and Technology Research Foundation (FSTRF)
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900 x7260
Email: zimmer@fstrf.org

Christina Reding, M.P.H.
Frontier Science and Technology Research Foundation (FSTRF)
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900, x7339
Email: reding@fstrf.org

Laboratory Data Managers
Katelyn Hergott, M.P.H.
Frontier Science and Technology Research Foundation (FSTRF)
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900, x7212
Email: hergott@fstrf.org

Clinical Trials Specialists
Anne Coletti, M.S.
FHI 360
PO Box 21059
Durham, NC 27703
Phone: (919) 544-7040, x11238
Email: acoletti@fhi360.org

Charlotte Perlowski, M.S.P.H.
FHI 360
PO Box 21059
Durham, NC 27703
Phone: (919) 544-7040, x11480
Email: cperlowski@fhi360.org
Protocol Statisticians
Camlin Tierney, Ph.D.
Statistical & Data Analysis Center
Harvard TH Chan School of Public Health
FXB Building Room 611
651 Huntington Avenue
Boston, MA 02115-6017
Phone: 617-432-0547
Email: tierney@sdac.harvard.edu

Bryan Nelson
Statistical & Data Analysis Center
Harvard TH Chan School of Public Health
FXB Building Room 625
651 Huntington Avenue
Boston, MA 02115-6017
Phone: 617-432-7130
Email: bnelson@sdac.harvard.edu

Protocol Pharmacist
Lynette Purdue, Pharm.D.
Contractor
DAIDS/NIAID/NIH
5601 Fishers Lane, RM 9E28
MSC 9830
Rockville, MD 20852-9830
Phone: 240-627-3061
lpurdue@niaid.nih.gov

Field Representative
Chivon D. Jackson, R.N., B.S.N., C.C.R.P.
Study Coordinator
Baylor/Texas Children's Hospital
Allergy and Immunology
6621 Fannin Street, MC: FC330.01
Houston, TX 77030
Phone: 832-824-1339
E-mail: cdmcmull@texaschildrenshospital.org

Protocol Virologist
Deborah Persaud, M.D.
Johns Hopkins University
Department of Pediatric Infectious Diseases
720 Rutland Avenue
Ross Building, Room 1170
Baltimore, MD 21205
Phone: (443) 287-3733
E-mail: dpers@jhmi.edu

Protocol Immunologist
Katherine Luzuriaga, M.D.
UMass Center for Clinical and Translational Research
University of Massachusetts Medical School
Biotech II, Suite 318, 373 Plantation Street,
Worcester, MA 01605
Phone: 508-856-6282
E-mail: katherine.luzuriaga@umassmed.edu

Rebecca LeBlanc
Frontier Science and Technology Research
Foundation, Inc.
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900
Email: leblanc@fstrf.org

Investigators
Diana Clarke, Pharm.D.
Section of Pediatric Infectious Diseases
Boston Medical Center
670 Albany Street, 6th Floor
Boston, MA 02118
Phone: 617-414-7508
E-mail: diana.clarke@bmc.org

Elizabeth (Betsy) McFarland, M.D.
University of Colorado School of Medicine
Pediatric Infectious Diseases
Children's Hospital Colorado
13123 East 16th Avenue, B055
Aurora, CO 80045
Phone: 303-724-3447
Email: betsy.mcfarland@ucdenver.edu

Theodore Ruel, M.D.
Assistant Professor
Division of Infectious Disease
Department of Pediatrics
UCSF Benioff Children’s Hospital
University of California, San Francisco
500 Parnassus Avenue
San Francisco, CA 94143-0113
Phone: 415-476-9197
E-mail: Ruelt@peds.ucsf.edu

Stephen Spector, M.D.
University of California, San Diego
Department of Pediatrics
Stein Clinical Research Building, Room 430
9500 Gilman Drive
MC 0672
La Jolla, CA, 92037-0672
Phone: 858-5347055
Email: saspector@ucsd.edu

Katherine Luzuriaga, M.D.
UMass Center for Clinical and Translational Research
University of Massachusetts Medical School
Biotech II, Suite 318, 373 Plantation Street,
Worcester, MA 01605
Phone: 508-856-6282
E-mail: katherine.luzuriaga@umassmed.edu
IMPAACT P1115
VERY EARLY INTENSIVE TREATMENT OF HIV-INFECTED INFANTS TO ACHIEVE HIV REMISSION: A PHASE I/II PROOF OF CONCEPT STUDY

KEY DEFINITIONS

*In utero* HIV infection is defined as at least one positive nucleic acid test from a blood specimen collected within 48 hours of birth, confirmed with a second positive nucleic acid test from a separate blood specimen.

HIV remission is defined as having no confirmed plasma HIV RNA greater than or equal to the limit of detection (LOD) of the assay through 48 weeks of ART cessation.

Postmenstrual age is calculated by adding postnatal age to gestational age at birth.

ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral Therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate Aminotransferase</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>CHAPAS-1</td>
<td>Children with HIV in Africa – Pharmacokinetics and Adherence of Simple Antiretroviral Regimens</td>
</tr>
<tr>
<td>CHER</td>
<td>Children with HIV Early Antiretroviral Therapy</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CLIA</td>
<td>Clinical Laboratory Improvement Act</td>
</tr>
<tr>
<td>CMC</td>
<td>Clinical Management Committee</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRPMC</td>
<td>Clinical Research Products Management Center</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
</tr>
<tr>
<td>DACS 095</td>
<td>Nevirapine Pharmacokinetics in Newborns and Infants: A Population Analysis</td>
</tr>
<tr>
<td>DAIDS</td>
<td>Division of AIDS</td>
</tr>
<tr>
<td>DBS</td>
<td>Dried Blood Spot</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>EAE</td>
<td>Expedited Adverse Event</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>EQA</td>
<td>External Quality Assurance</td>
</tr>
<tr>
<td>FDA</td>
<td>(United States) Food and Drug Administration</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HPTN 012</td>
<td>Phase IIB Trial to Determine the Efficacy of Oral AZT and the Efficacy of Oral Nevirapine for the Prevention of Vertical Transmission of HIV-1 Infection in Pregnant Ugandan Women and Their Neonates</td>
</tr>
<tr>
<td>HPTN 046</td>
<td>Phase III Trial to Determine the Efficacy and Safety of an Extended Regimen of Nevirapine in Infants Born to HIV-Infected Women to Prevent Vertical HIV Transmission During Breastfeeding</td>
</tr>
</tbody>
</table>
IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Group
NICHHD/HPTN 040: Phase III Randomized Trial of the Safety and Efficacy of 3 Neonatal ARV Regimens for Prevention of Intrapartum HIV-1 Transmission
P1066: A Phase I/II, Multicenter, Open-Label, Noncomparative Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiretroviral Activity of Raltegravir (Isentress™, MK-0518) in HIV-1 Infected Children and Adolescents.
P1097: Raltegravir Pharmacokinetics and Safety in Neonates
P1110: A Phase I Trial to Evaluate the Safety and Pharmacokinetics of Raltegravir in HIV-Exposed Infants at High Risk of Acquiring HIV-1 Infection

Terms:
IQA: DAIDS Immunology Quality Assurance program
IRB: Institutional Review Board
IRIS: Immune Reconstitution Inflammatory Syndrome
LAR: Legally Authorized Representative
LOD: Limit of Detection (for an HIV RNA assay)
LPC: Laboratory Processing Chart
LPV/r: Lopinavir/Ritonavir
MOP: Manual of Procedures
NIAID: National Institute of Allergy and Infectious Diseases
NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI: Nucleoside/Nucleotide Reverse Transcriptase Inhibitor
NVP: Nevirapine
OPH03: Optimizing Pediatric HIV-1 Therapy 03
PACTG 345: Phase I/II Study of Ritonavir Therapy in HIV-1 Infected Infants
PACTG 356: Early Intensive Antiretroviral Combination Therapy in HIV-1 Infected Infants and Children
PACTG P1030: Phase I/II Study of Lopinavir/ritonavir in HIV-1 Infected Infants < 6 Months of Age
PCR: Polymerase Chain Reaction
PCP: Pneumocystis Carinii Pneumonia
PENTA: Paediatric European Network for the Treatment of AIDS
PENTA 11: Treatment Interruption in Children with Chronic HIV-Infection: The TICCH Trial
PI: Protease Inhibitor
PID: Patient Identification Number
PK: Pharmacokinetic
PRIMO-SHM: No Treatment versus 24 or 60 Weeks of Antiretroviral Treatment during Primary HIV Infection: The Randomized Primo-SHM Trial
PRO: Division of AIDS Protocol Registration Office
PTC: Post Treatment Controllers
PTI: Planned Treatment Interruption
RAL: Raltegravir
RE: Regulatory Entity
RNA: Ribonucleic Acid
RSC: Regulatory Support Center
SES: Subject Enrollment System
SETPOINT: Effect of Immediate Versus Deferred Antiretroviral Therapy on Virologic Set Point in Recently HIV-1-Infected Individuals: The Setpoint Study/ACTG A5217
SID: Study Identification Number
SMART: Strategies for Management of Antiretroviral Therapy
SMC: Study Monitoring Committee
SPARTAC: Short Pulse Anti-Retroviral Therapy At seroConversion
STI  Structured Treatment Interruption
SUSAR  Suspected Unexpected Serious Adverse Reaction
TNA  Total Nucleic Acid
US  United States
VISCONTI  Virological and Immunological Studies in CONtrollers After Treatment Interruption
VQA  DAIDS Virology Quality Assurance program
WHO  World Health Organization
ZDV  Zidovudine
IMPAACT P1115
VERY EARLY INTENSIVE TREATMENT OF HIV-INFECTED INFANTS
TO ACHIEVE HIV REMISSION: A PHASE I/II PROOF OF CONCEPT STUDY

SCHEMA

DESIGN
Phase I/II proof of concept exploratory study

SAMPLE SIZE
Up to 905 mother-infant pairs are expected to be enrolled:

- 460 mother-infant pairs were enrolled under protocol Version 1.0 to identify 54 infants with in utero HIV infection
- Approximately 445 mother-infant pairs are expected to be enrolled under protocol Version 2.0 to identify approximately 45 infants with in utero HIV infection

POPULATION
Cohort 1: Infants at high risk for in utero HIV infection; defined as having been born to a mother with presumed or confirmed HIV infection who did not receive any antiretrovirals during pregnancy; enrolled with their mothers within 48 hours of birth.

Cohort 2: In utero HIV-infected, antiretroviral therapy (ART)-started infants; defined as having at least one positive HIV nucleic acid test (NAT) from a sample collected within 48 hours of birth outside the study and having initiated a qualifying ART regimen within 48 hours of birth outside the study; enrolled with their mothers within 10 days of birth.

See Section 4.0 for maternal and infant eligibility requirements.

INFANT STUDY REGIMENS
Three early intensive therapy regimens will be assessed:

- **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)

See Section 3.0 for cohort assignment to each regimen and Section 5.0 for detailed information on each regimen.
**STUDY DESIGN**

**Step 1:** Cohort 1 infants will be enrolled in Step 1 for evaluation of HIV infection and initiation of early intensive therapy within 48 hours of birth. Infants in whom *in utero* HIV infection is excluded will switch from the study regimen to standard perinatal prophylaxis per local guidelines within two weeks; these infants will continue in Step 1 safety monitoring for two additional weeks, undergo final HIV testing at approximately 12 weeks of age, and then exit the study. Infants in whom *in utero* HIV infection is confirmed will enter Step 2 at least two weeks after enrollment in Step 1.

**Step 2:** Cohort 1 infants identified with *in utero* HIV infection and Cohort 2 infants will enter Step 2 and receive the study regimen in this step for up to 192 weeks. Beginning at Step 2 Week 84, children who achieved HIV RNA suppression by Week 24, and maintained suppression thereafter, with no HIV RNA detected at or after Week 48, will be evaluated for possible treatment cessation.

**Step 3:** Children in Step 2 who meet criteria for treatment cessation will enter Step 3, stop ART, and be closely monitored for viral rebound for up to five years in this step.

**Step 4:** Children who experience viral rebound in Step 3 will enter Step 4, restart ART, and be closely monitored for viral re-suppression on ART until five years of age or six months after re-suppression, whichever is later.

**STUDY DURATION**

Accrual of mother-infant pairs under protocol Version 2.0 is expected to require up to three years (from the date of first enrollment). HIV-uninfected infants will be followed for 12 weeks. HIV-infected infants will be followed for up to 192 weeks in Step 2 (on ART); those entering Step 3 will be followed for primary endpoint ascertainment at 48 weeks and for up to a total of five years (off ART) in this step.

**PRIMARY OBJECTIVE**

- To assess HIV remission among neonates with *in utero* HIV infection who initiate early intensive therapy within 48 hours of birth. HIV remission is defined as having no confirmed plasma HIV-1 RNA greater than or equal to the limit of detection of the assay (≥ LOD) through 48 weeks of ART cessation.

**SECONDARY OBJECTIVES**

- To assess the safety and tolerability of early intensive therapy regimens in neonates and young infants.
- To assess, by regimen (Regimen 1L separately from Regimens 2R+2RV combined), the proportion of infants receiving early intensive therapy who achieve viral suppression (plasma HIV-1 RNA < LOD) at Week 24.
- To assess, by regimen (Regimen 1L separately from Regimens 2R+2RV combined), the proportion of infants receiving early intensive therapy who meet virologic and immunologic criteria for treatment cessation.
- To assess, by regimen (Regimen 1L separately from Regimens 2R+2RV combined), the relationship between time to achieve confirmed viral suppression (plasma HIV-1 RNA < LOD) and meeting the virologic and immunologic criteria for treatment cessation.
• To assess the extent of HIV persistence in infants who achieve HIV remission.
• To evaluate immune activation and host and viral determinants, including maternal factors and HIV-specific immune responses, associated with HIV remission.
• To assess biomarkers of HIV reservoir size among infants receiving early intensive therapy (including but not limited to proviral HIV DNA load and HIV serostatus).
• To assess resistance to ARVs included in the study regimens and to VRC01.
• To describe RAL and VRC01 exposures in neonates and young infants.

EXPLORATORY OBJECTIVES
• To observe the frequency of intrapartum or early breast milk infection (assessed at approximately 12 weeks of age) following receipt of early intensive therapy.
• To explore rates of HIV and cytomegalovirus co-infection in neonates at high risk of perinatal HIV infection.
1.0 INTRODUCTION

1.1 Background and Rationale

The capacity of the human immunodeficiency virus (HIV) to establish latency in long-lived cells, particularly in resting memory CD4+ T cells, precludes virus eradication with current combination antiretroviral therapy (ART) (1). HIV latency in resting memory CD4+ T cells promotes viral quiescence, which renders latently infected CD4+ memory cells non-susceptible to antiretroviral drugs or HIV-specific immunity. These memory CD4+ T cells harbor latent HIV genomes and arise during development of immunologic memory (1). Formation of the latent reservoir in a developing immune system has important implications for the size and distribution of this reservoir in HIV-infected infants (2-4). This feature distinguishes the latent HIV reservoir formation and its maintenance in pediatric HIV infection from HIV-infected adults and has implications for targeting viral reservoirs formation with very early therapy to achieve HIV remission for pediatric populations.

There remain few cases of HIV remission and only a single case of HIV cure to date (5). The single case of HIV cure in an adult (the “Berlin patient”) provided proof of concept that HIV can be eradicated from the body, including the central nervous system, whereby ART can be discontinued without viremic rebound (6, 7). HIV cure occurred in this individual following treatment for acute myelogenous leukemia with total ablative chemotherapy, irradiation and repeat stem cell transplantation with donor cells homozygous for CCR5 delta32, accompanied by graft versus host disease. This case demonstrates that replication-competent HIV reservoirs can be reduced or cleared sufficiently to permit ART discontinuation without subsequent viremic rebound for at least seven years thereafter (7). The added benefit of sustained virologic control from receipt of donor cells naturally resistant to CCR5-utilizing HIV variants is supported by the recent report of eventual viremic rebound in two HIV-infected adults following reduced intensity allogeneic bone marrow transplantation with CCR5-wild type donor cells. Return of viremia in these two cases at 12 and 32 weeks post-ART cessation highlights the current lack of biomarkers predictive of persistent HIV with capacity to re-ignite infection. In these two patients, circulating blood samples failed to reveal persistent HIV infection when tested using ultrasensitive HIV DNA and replication-competent viral outgrowth assays in large blood volumes (8).

A case of prolonged HIV remission (no viremic rebound within one year) was reported in a United States (US) born child (the “Mississippi Child”) who was treated with a three-drug NVP-based ART regimen by 31 hours of life for high-risk HIV-exposure from untreated maternal infection (9). Longitudinal follow-up revealed eventual return of viremia at 46 months of age after being off ART for nearly 2.3 years (10).

In this infant, plasma viral load reached undetectable levels by 28 days of age on ART and remained undetectable even when ART was discontinued at age 18 months (9). This child was intensively followed off ART because of the unusual finding of no rebound viremia despite being off ART for five months. At the first report, the child had remained aviremic off ART for 12 months. Of note, there were no detectable HIV-specific immune responses or HLA-alleles known to confer spontaneous control of HIV replication. Together, these findings were interpreted to reflect control of viremia from lack of development of replication-competent HIV reservoirs (9).

A follow-up study reported on persistent lack of detectable replication-competent HIV reservoirs and sustained virologic control with absent viremia to <0.4 copies/mL off ART for 22 months at age 40 months (11). However, proviral DNA was intermittently detected at extremely low levels near limits of detection of the quantitative HIV DNA droplet digital PCR assay and virologic
control was sustained with continued virologic remission. The child was monitored closely every 4-8 weeks. During routine follow-up care at age 3.8 years of age, coinciding with 2.3 years of virologic remission, the child had clinically asymptomatic viremia above the limit of detection of clinical viral load assays that was subsequently confirmed 72 hours later. ART was restarted, and the child exhibited a prompt response to ART with a 0.6-log decline in plasma viral load within 72 hours of ART. In addition, the CD4 counts returned to baseline normal levels within 72 hours of ART. Phylogenetic analysis confirmed the source of rebounding virus was transmitted virus from the mother (9), providing evidence for marked diminution in reservoir size to permit HIV remission for over two years. The re-emergence of viremia in this child provides further support that viral remission is achievable in perinatal infection through time-limited very early ART, although the exact timing of ART initiation and duration of ART required to achieve cure is unknown. The P1115 study will specifically address the hypothesis that very early therapy of HIV-infected neonates substantially limits the establishment of HIV reservoirs, including the long-lived resting memory CD4+ T cell latent reservoir, to permit long-term control of HIV replication off ART, leading to HIV remission.

Importantly, there are converging data that early therapy during acute HIV infection in adult and children quantitatively modifies HIV persistence and HIV-specific immune responses (12-14), although the extent to which ART can be discontinued in these settings as in the Mississippi Child, is uncertain.

Follow-up studies of early-treated infants virologically suppressed through adolescence have demonstrated lower levels of replication-competent viral reservoirs than in later-treated children (15). Moreover, Luzuriaga (16) and colleagues have shown that the absence of HIV-specific immune responses may be a marker for strict control of HIV replication following early therapy. A study of HIV persistence in four HIV-infected youth with continuous suppression of HIV replication for 10 or more years after uninterrupted ART initiated before three months of age demonstrated low levels of circulating HIV provirus, undetectable plasma RNA by ultrasensitive assays, lack of replication-competent virus, and lack of HIV-specific immune responses (17). Circulating HIV proviral DNA levels were lower than those reported in the VISCONTI Cohort of adult post-treatment controllers (PTCs; see below) (18, 19): viral decay over time was also observed. Low circulating proviral reservoirs following early ART was also reported in early-Thai and South African children by 8 years of age (12, 20). Evidence for decreasing concentrations of infected cells over the time course of ART with early ART initiation was confirmed in a larger longitudinal study of perinatally-infected children (PHACS Cohort) (21). Association between low proviral load and restricted HIV-1 antibody responses was also observed in the PHACS cohort study (21). Data from these children, along with those from the Mississippi Child and the Berlin Patient presented above, suggest that persistent HIV-specific immune responses may be sensitive indicators of residual virus producing cells (and that conversely, lack of HIV-specific immune responses may indicate controlled HIV replication).

A French perinatally HIV-infected adolescent who started ART at three months of age was identified as a PTC with control HIV viremia to clinically undetectable levels for over 11 years off ART (treatment was discontinued by the family between 5.8 and 6.8 years of age). This case showed evidence of prolonged HIV remission even in the setting of detectable HIV DNA and HIV antibody. The case adds further evidence that early treatment may allow a balance of immune control to facilitate prolonged periods of viral suppression without ARV in certain individuals (22).
Biomarkers of HIV persistence that are predictive of delayed rebound viremia are lacking (5). Proviral load is associated with time to viral rebound in HIV-infected adults treated during primary HIV infection (23). Low proviral load was also observed in PTCs (19). A state of nondetectable HIV DNA is observed amongst children treated early in the course of infection when tested by clinical assays. In a report (14), four perinatally HIV-infected children (2.5-7.5 years of age) from the Canadian registry received the same triple ART regimen from birth as the Mississippi Child. While these four children had nondetectable proviral reservoirs at <2.6 copies/million in circulating CD4+ T cells, and were HIV-seronegative, persistent cell-associated HIV RNA was found, indicating persistence of transcriptionally active viral genomes. A similar finding of persistence of low levels (5 copies/million PBMCs) of cell-associated HIV RNA transcripts was found after 7-8 years of uninterrupted ART in early-treated children (20). These cases highlight the need for ongoing studies of HIV persistence in children receiving early and very early treatment to identify biomarkers of HIV remission with the goal of transforming HIV into a time-limited infection without a lifetime of treatment. Together, these studies emphasize the need for a clinical trials approach to address these questions systematically to advance the field while minimizing safety risks.

Evidence of early treatment limiting HIV reservoirs has emerged from case studies in adults (18, 19); 5-15% of HIV-infected adults treated during early infection have maintained control of virus replication to clinically undetectable levels after time-limited ART. Post-treatment controllers (PTCs) have very low levels of cell-associated HIV provirus that decay even while off ART. PTCs also have lower levels of activated CD8+ T cells and HIV-specific T cell responses compared with the 1-5% of HIV-infected adults who spontaneously control HIV replication to clinically undetectable levels in the absence of antiretroviral drugs (“Elite Controllers”) (24); specific HLA-alleles (HLA-B57 and HLA-B27) and vigorous HIV-specific T cell responses are implicated as the mechanism of virologic control in “Elite Controllers.” To date, post-treatment control in perinatal infection is not well-defined. A single case of post-treatment control in a perinatally-infected adolescent was recently reported (22).

Currently, one limitation to widespread implementation of immediate or very early therapy in HIV-infected infants is the lack of a widely available point-of-care nucleic acid tests to quickly identify HIV infection in HIV-exposed neonates, although the field is rapidly evolving. Presently, given the likelihood that HIV establishes persistent infection within days of infection, in viral reservoirs that preclude HIV remission and cure, it will be critical in this study to empirically start therapy within the first 1-2 days of life, while awaiting confirmation of infection by standard nucleic acid testing.

Infants are also at risk for acquiring HIV during the birth process and in the early postpartum period through breastfeeding, particularly if maternal viremia is uncontrolled. Infants who escape in utero infection but become infected during birth or in the early postpartum period through breastfeeding will test HIV-negative at birth but subsequently test HIV-positive, usually by six weeks of age. Initiation of early intensive therapy within 48 hours of birth may delay detection of intrapartum or breast milk HIV transmission in the first six weeks of life through early suppression of virus replication. Current HIV nucleic acid testing platforms may not be sensitive enough to detect low levels of HIV DNA or RNA while the infant is receiving ARVs; therefore, additional testing may be required to fully exclude HIV infection. Repeat testing at 12 weeks of age identified an additional 30% of infants who had tested negative at six weeks of age in the NICHD/HPTN 040 trial of enhanced prophylaxis initiated within 48 hours of birth in high-risk, formula-feeding infants, suggesting a delay in diagnosis because of low-infected cell concentrations following enhanced prophylaxis. Additional testing through 12 weeks of age will
provide insights into detection of intrapartum and early breastmilk infection in the setting of enhanced prophylaxis.

1.2 Treatment Cessation to Assess HIV Remission

Given the current lack of biomarkers predictive of HIV remission, it will be essential to discontinue ART, under closely monitored follow-up, to test the hypothesis that early intensive therapy sufficiently limits the establishment of persistent infection in viral reservoirs to enable HIV remission. (25). All previous and current ART guidelines for all age groups recommend continuous lifelong ART, due to the viral rebound that ensues (within 2-4 weeks) when ART is stopped. The rebounding virus is thought to come from the persistence of HIV in replication-competent forms in viral reservoirs. The incorporation of treatment cessation as a strategy to determine HIV remission as a consequence of novel therapeutic interventions is an area of ongoing discussion in cure-related clinical trials. However, given the current lack of predictors of HIV remission, planned treatment interruption with close monitoring has been incorporated into adult clinical trials (26) to assess therapeutic efficacy of cure-related interventions. This approach has been well tolerated and remains the only way to determine whether newer therapeutic approaches to HIV will decrease HIV reservoirs sufficiently and preserve the immune system to lead to sustained control of viremic rebound off ART.

1.3 Planned Treatment Interruption in HIV-Infected Children and Adults Treated during Chronic HIV Infection

There is long-standing experience with planned treatment interruption (PTI) also referred to as structured treatment interruption (STI) both in HIV-infected adults, adolescents and children effectively treated during acute or chronic infection. The study that has informed long-term outcomes of PTI in HIV-infected patients is the Strategies for Management of Antiretroviral Therapy (SMART) Study (27). This large multi-center trial comparing CD4 guided PTI with continuous ART and enrolling 5472 adults was stopped because of an unexpected increase in risk of opportunistic infection or death in participants undergoing PTI, with non-infectious renal, cardiovascular and hepatic disease contributing most to the primary endpoint. However, in children, PTI has thus far been safe in two randomized pilot studies, PENTA 11 (Treatment Interruption in Children with Chronic HIV Infection: The TICCH Trial) in Europe and the OPH03 (Optimizing Pediatric HIV-1 Therapy 03) study in Kenya, which evaluated CD4-driven planned treatment interruptions in older HIV-infected children. Neither trial showed significant morbidity differences between their randomized arms (28, 29).

In the PENTA 11 pilot trial, 109 children with perinatal HIV infection were randomized to PTI or continuous ART at a median age of 9.3 years. All had viral load < 50 copies/mL and CD4 > 30%. Thirty-two of 51 on PTI successfully completed 48 weeks of follow-up without meeting criteria to restart ART during interruption. PTI was not associated with adverse events. Younger age and higher nadir CD4% predicted both remaining off ART for at least 48 weeks and better CD4% recovery following PTI (28). PENTA 11 established the safety of PTI in children. Of note, no neurodevelopmental consequences were noted after PTI in the PENTA 11 study (30, 31). A follow-up study, conducted 2 years later, again showed no consequences of PTI (31). In the OPH03 study in Kenya, infants commenced ART at a median age of 5 months. Treatment was interrupted after 24 months, with 14 of 21 children reaching CD4 restart criteria within three months of PTI. In a small study of adolescents (N = 14) who were well-controlled on ART and underwent increasing sequential cycles off ART compared to 21 adolescents on continuous ART, a subset who were exposed to ≥ 13 progressively lengthening PTI cycles were able to stay off ART for more than 27 days. In this study, enhanced HIV-specific immune responses correlated
with declining viral load (32, 33). One outcome of this cycling strategy, however, was the development of antiretroviral drug resistance mutations in 3 of the 14 study participants. In P1115, the treatment cessation will occur at a defined period and participants will be followed closely and restarted on their ART regimen if rebound viremia ensues.

1.4 Planned Treatment Interruption After Acute Infection

Treatment interruption in the setting of treatment initiation during acute infection appears to be different. Three adult studies addressing early ART followed by treatment interruption showed benefit with higher CD4 count and lower viral set point but did not show clinical benefit (34-36). The largest and best conducted study was the randomized Short Pulse Anti-Retroviral Therapy At seroConversion (SPARTAC) trial, identifying adults within 6 months of infection. Participants received either ART for 12 or 48 weeks followed by PTI, or standard of care. Early ART for 48 weeks favorably altered the trajectory of CD4 depletion and HIV RNA elevation, the two main markers of HIV disease progression. In a secondary analysis, more sustained virological control was directly related to closeness of ART initiation to time of primary infection (34). Two relatively small studies, the Setpoint/ACTG A5217 study (Effect of Immediate Versus Deferred Antiretroviral Therapy on Virologic Set Point in Recently HIV-1-Infected Individuals: The Setpoint study/ACTG A5217) and Primo-SHM trial (No Treatment versus 24 or 60 Weeks of Antiretroviral Treatment during Primary HIV Infection: The Randomized Primo-SHM Trial) also showed a lower average viral load after early time-limited ART compared to deferred ART (35, 36).

The study shedding new light on early therapy and the potential to stop ART is the Virological and Immunological Studies in CONtrollers after treatment interruption (VISCONTI) cohort study from France. After primary ART for a median of 5 years, 5 of 32 adults controlled HIV replication for more than 6 years post PTI (18). In an update, they describe immunological and virological control in 14 patients off ART for a median of 76 months, possibly explained by preservation of central memory CD4 cells. The VISCONTI cohort is phenotypically different from long-term non-progressors where factors such as HLAB27/57 phenotype are relevant (19).

There is extensive experience with treatment cessation in the context of early ART (within 3 months of life) in children. The Children with HIV Early Antiretroviral (CHER) trial was an open label 3-arm trial in HIV-infected asymptomatic infants aged < 12 weeks with CD4% ≥ 25%. The main hypothesis was that early limited ART started close to primary infection would prevent disease progression and safely allow a subsequent period off ART, thus preserving future treatment options when compared with deferred ART. In the trial, 377 infants were randomized to deferred (ART-Def) or immediate ART for 40 weeks (ART-40W) or 96 weeks (ART-96W), followed by PTI. Criteria for ART initiation in ART-Def and re-initiation after interruption were CD4% < 25% in infancy; otherwise < 20% or CDC severe stage B or stage C disease. First line ART was lopinavir/ritonavir (LPV/r), zidovudine (ZDV) and lamivudine (3TC). The trial commenced in mid-2005. HIV DNA PCR was undertaken from four weeks of age with HIV infection confirmed by a quantitative HIV RNA >1000 copies/ml. Median age at baseline was between 7.1 and 7.5 weeks of age. In June 2007, an interim analysis revealed that early ART reduced mortality by 74% (37). In the full results, after a median of 5 years on study, the benefit of early limited versus deferred continuous ART was confirmed (38). Clinical endpoints, mainly death, occurred early and remained significantly higher in the deferred arm despite a longer period on continuous ART. Outcomes were marginally better with longer primary therapy (ART-96W). Children in ART-96W remained off ART during PTI for a median of 70 (95% CI: 35 to 109) weeks compared to 33 (95% CI: 26 to 45) weeks in ART 40W (p = 0.13), also with fewer primary endpoints and reduced hospitalization. It is plausible that a longer period of primary ART
in *CHER* might have sustained better long-term outcomes following interruption. The study was not powered to allow comparison between the ART-40W and ART-96W arms. There were nine cases of HIV encephalopathy in ART-Def, five in ART-40W and two in ART-96W, again suggesting the importance of early ART for a longer period.

A single child randomized to the ART-40W arm remained off ART without detectable HIV RNA in plasma for 8.5 years (39). The quantity of HIV DNA detected at time of interruption (a year of age) and most recent testing at 9.5 years of age revealed 5 HIV-1 copies per $10^6$ PBMCs. Detailed analyses are underway, but it is likely that this child has host factors that contributed to post-treatment control as the plasma HIV RNA level declined from >750,000 HIV RNA copies per mm$^3$ at day 32 of life to 150,000 copies per mm$^3$ by day 60 when ART was started (39).

During the interruption phase, plasma samples were stored at the onset of interruption, eight weeks later, and then three-monthly during interruption. Viral rebound was studied in 183 of 245 children who interrupted ART. The study sample was limited to those with a viral load below 400 HIV RNA copies per mm$^3$. The cumulative probability of rebound was 70% by two months, 80% by four months, 94% by six months and 99% by eight months (40). Only the one child described above (39), had no rebound.

### 1.5 Timing of Treatment Cessation

The optimal time to cease ART after very early therapy to assess HIV remission is unknown. In the Mississippi Child, who experienced prolonged HIV remission (9), adherence was suboptimal at around 15 months of age and ART was discontinued by 18 months of age. It is unclear if increased duration of therapy greater than 18 months would have further reduced the chances of rebound or prolonged the time to rebound or, alternatively, that limiting the time of viremia in the first days following birth is the key factor or a combination of both. Multiple factors may contribute to estimates of time to clearance of pre-existing HIV-infected cells before ART was started. These include the half-lives of the infected cell populations and the total body burden of HIV virions, some of which can be trapped on follicular dendritic cells for years. Perelson and Ho initially estimated (41) that continuous ART for up to three years may lead to full clearance of HIV-infected cells and free virions bound to follicular dendritic cells to achieve cure if very long-lived reservoirs were not present. With the assumption that very early treatment substantially reduces HIV reservoirs, including those in central memory CD4+ T cells, the duration of ART to promote viral remission is unclear; however, stopping of ART will first be considered in P1115 at approximately two years of age. It is expected that the feasibility of stopping ARV treatment by two years of age will vary significantly by the timing and duration of in utero infection during gestation prior to birth and the viral burden and state of the virus (quantity of integrated virus) present in the infant prior to initiation of treatment. Hence, evaluation of biomarkers of the state of HIV persistence will begin prior to two years of age (beginning at Step 2 Week 84) and may continue for up to two additional years (through Step 2 Week 192) to assess eligibility for stopping ART. The biomarkers that will be used to determine if ART should be discontinued are detailed in the Step 3 eligibility criteria (see Section Must have met ALL of the following additional criteria while in Step 2, obtained at $\geq$ Step 2 Week 84 and $\leq$ Step 2 Week 192:) and include proviral load assessed by droplet digital HIV DNA PCR. Any study participant whose ART is discontinued will be monitored closely for viral rebound.

Mathematical and statistical models have been used to predict time to viral rebound following ART cessation in HIV-infected patients relative to reservoir size (42). This model also has been used to provide guidance around frequency of viral load testing off ART to capture early viral rebound in HIV remission and cure trials. It is well established that HIV rebounds to clinically
detectable levels within 2-4 weeks of ART cessation in most patients. In the Mississippi Child, the reduction in latent reservoir size achieved with very early ART to enable 27 months of virologic remission is estimated to be 2.5 logs smaller than the typical adult size. In the “Boston patients” and “Berlin patient,” the estimated reduction in the latent reservoir to afford 3 and 8 months and greater than 8 years of virologic remission, respectively, was 2.0 and 3.5 logs, respectively (42). Together, these data support the notion that reservoir size as measured by HIV DNA may be a useful biomarker to guide ART cessation in perinatal HIV infection.

In P1115, the frequency of monitoring for viral rebound off ART is based on feasibility of testing and mathematical models by Hill et al. describing this probability. Given that most patients rebound within 2-4 weeks of ART cessation, children in this study will be monitored with HIV RNA testing at Weeks 1, 2, 3, 4, 6, and 8 after stopping ART, and every four weeks thereafter.

1.6 Rationale for Enhancing Antiviral Options for Very Early Treatment of Perinatal HIV Infection.

This study focuses on the effect of early intensive therapy (initiated within the first 48 hours of birth) on the likelihood of achieving HIV remission. In a similar cohort of infants enrolled in NICHD/HPTN 040, 93 infants with in utero infection had plasma HIV viral loads within 48 hours of birth ranging from several hundred to several million RNA copies/mL, with a median of 100,000 copies/mL. Plasma viral load was reduced by at least 1.5 log by two weeks of age with combination ARV prophylaxis consisting of either ZDV with three doses of NVP or with ZDV, 3TC, and nelfinavir given during the first two weeks of life. Plasma levels of NVP were 100 ng/ml (10 times greater than inhibitory concentrations) for a minimum of 10 days with the three-dose regimen. However, despite the significant reduction of viral load in all infants receiving two or more drugs, none of the in utero infected infants achieved viral suppression by the two-week time point. Furthermore, rebound viremia reached high levels within 4-6 weeks following discontinuation of the combination prophylactic regimen. Therefore, early use of combination ARVs to prevent transmission is insufficient to achieve HIV remission. A more potent and prolonged antiviral effect is likely needed (43).

The challenge of providing adequate drug concentrations with potent antiviral coverage in infants during acute/primary HIV infection was highlighted in PACTG 345, A Phase I/II Study of Ritonavir Therapy in HIV-1 Infected Infants. Here, a negative correlation between baseline plasma HIV RNA levels and the slope of decay of plasma viremia was demonstrated, likely reflective of suboptimal antiviral drug concentrations coupled with very high pretreatment baseline plasma levels (44). The potential effect of even a small decrease in phase 1 decay for infants with high plasma virus levels may be significant, as it could delay prompt control of virus replication with potential to select for drug resistant virus and lead to rebound viremia.

The time to achievement of undetectable plasma viral load was highly correlated with the size of the resting CD4+ T cell latent HIV reservoir at two years of age in infants less than six months of age participating in the IMPAACT P1030 study of early ART with two nucleosides in combination with LPV/r (15). In addition, pre-ART HIV-infected cell concentrations were correlated with time to achieve undetectable plasma viral loads and with post-ART infected cell concentrations persisting through 2 years of age. With the goal of rapidly reducing HIV viral load to undetectable levels and maintaining durability in infants with acute primary HIV infection, it is essential to provide a regimen with known potent antiviral activity in neonates.

Studies of very early treatment to achieve HIV remission in infants are limited by the paucity of safety and PK data on ARVs for neonates. Due to the limitation in neonatal PK data and available pediatric formulation of antiretroviral drugs along with potential early toxicity, the approach taken under Version 1.0 of the P1115 protocol was to initiate empiric ART using antiretroviral
drugs with a known track record in neonatal prophylaxis (ZDV, 3TC, NVP) and based on the experience of the Mississippi Child. Among all infants enrolled under protocol Version 1.0 through February 2017 (n=255), 29 (11%) experienced a Grade 3 or higher hematologic laboratory event assessed as possibly, probably or definitely related to study drug. Among HIV-exposed uninfected infants, who received the study drug regimen for 1-2 weeks, 16 of 225 (7%) experienced such an event; among HIV-infected infants, 13 of 30 (43%) experienced such an event. The hematologic events involved decreased absolute neutrophil counts and hemoglobin levels that, with one exception, were asymptomatic; in the case of the one exception, an HIV-infected infant experienced clinically significant anemia and was treated with a transfusion. Twelve of 13 HIV-infected infants with Grade 3 or higher hematologic events discontinued ZDV and switched to abacavir or stavudine. The events improved to grade 2 or lower within a median of 20 and 22 days for hemoglobin and absolute neutrophil count, respectively; the switch of ZDV to another NRTI resulted in resolution without significant interruption of ARV therapy.

As indicated above, Version 1.0 of this protocol specified use of ARVs with available data — ZDV, 3TC, and NVP — at therapeutic doses initiated within 48 hours of birth, with LPV/r at two weeks of age or 42 weeks postmenstrual age. One limitation of NVP-based initial ART is high prevalence of pre-existing NVP resistance coupled with early selection of drug-resistance with non-suppression (45). Thus far, experience with the NVP and LPV/r based regimen under protocol Version 1.0 has not shown consistent viral decay dynamics towards sustained viral suppression by 24 weeks of ART (unpublished data). This is required for transition to Step 3, in which evaluation for HIV remission will occur after sustained viral suppression. Together, these data indicate that more potent regimens will be needed for early curtailment of HIV replication and clearance of HIV-infected cells. Similar experience has been reported with very early NVP based ART in two other clinical studies (46).

Safety and PK data recently became available for the integrase inhibitor raltegravir (RAL) from the IMPAACT P1097 and P1110 studies (47) and RAL was subsequently approved by the US Food and Drug Administration (FDA) for treatment of neonates weighing at least 2 kg. Neonatal safety and PK data also recently became available for the broadly neutralizing antibody, VRC01, from the IMPAACT P1112 study (48). Both of these agents offer promise of a more potent approach towards more rapid control of HIV replication and elimination of HIV-infected cells and will be evaluated under protocol Version 2.0.

IMPAACT P1097, Raltegravir Pharmacokinetics and Safety in Neonates, examined the wash-out PK of RAL in infants born to mothers who were receiving RAL during pregnancy. In P1110, A Phase I Trial to Evaluate the Safety and Pharmacokinetics of Raltegravir in HIV-Exposed Infants at High Risk, the PK and safety of subsequent infant dosing with RAL oral granules during the first six weeks of life were studied. The unique mechanism of action of RAL to block viral integration into host DNA, along with its rapid effect on clearance of plasma viremia has potential to significantly alter reservoir dynamics in perinatal infection. With safety and PK data now available to guide dosing in neonates, RAL has been included in the early intensive therapy regimens planned to be evaluated under protocol Version 2.0 (see Section 5.1.2 for more detailed information on the Version 2.0 regimens for infected infants).

Inclusion of VRC01, which has demonstrated antiviral activity (49), in early intensive ART regimens may provide additional activity against circulating virus through potent neutralization. In addition, antibodies have the potential to eliminate cell-associated virus, as demonstrated in several non-human primate studies. A study of a combination of bNABs given within 24 hours post-exposure in non-human primates (NHP) demonstrated prevention of long term reservoir formation and viral eradication from multiple tissue sites (50). In another study, early
administration of a combination of bNAbs demonstrated sustained viral remission in a SHIV NHP model (51). Thus, VRC01 may contribute to reservoir reduction through virus neutralization and anti-viral activity in the tissues.

Because previous studies have established safety profiles for RAL and VRC01 (see 1.8 and 1.9), accrual of participants receiving the two RAL-based treatment regimens will occur concurrently. Based on regulatory and pharmacy considerations for VRC01 as well as operational considerations for the study, sites will be assigned to enroll participants receiving one regimen or the other. Site assignments to each regimen may be changed over time (e.g., to address lags in enrollment for one of the regimens) but at no time will any site be enrolling infants receiving both regimens concurrently.

1.7 Rationale for Nevirapine and Lopinavir/Ritonavir Dosing

Refer to protocol Version 1.0 for a detailed description of the rationale for NVP and LPV/r dosing specified for this study. The NVP dose evaluation performed under protocol Version 1.0 supported the NVP dosing specified in protocol Version 1.0 and continued under protocol Version 2.0 (52).

1.8 Rationale for Raltegravir Use in Children

RAL (Isentress™) is a potent and selective HIV-1 integrase inhibitor. Integrase, one of three HIV-1 enzymes required for viral replication, catalyzes the stepwise process which results in the integration of the HIV-1 DNA into the genome of the host cell. RAL inhibits HIV-1 replication by interfering with this process of integration. The drug is well tolerated with potent HIV-1 suppression demonstrated in treatment naïve and experienced adults and treatment experienced infants and children at least four weeks of age (14-19, 24, 25). In normal adults, approximately 7-14% of an administered RAL dose is excreted unchanged in urine. The primary route of RAL elimination is hepatic metabolism by UDP (uridine diphosphate)-glucuronosyltransferases (UGT), primarily UGT1A1 but with minor contributions from UGT1A3 and UGT1A9, followed by excretion of raltegravir-glucuronide via stool and urine (28). There is considerable variability in the PK of RAL. In adults, RAL has an initial (α) t ½ of approximately 1 hour and a terminal elimination (β) t ½ of approximately 7 to 12 hours (27).

RAL safety, tolerability, PK, and efficacy in infants and children were evaluated in IMPAACT P1066, A Phase I/II, Multicenter, Open-Label, Noncomparative Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiretroviral Activity of Raltegravir (Isentress™, MK-0518) in HIV-1 Infected Children and Adolescents. This study evaluated three RAL formulations across the pediatric age range and data from the study served as the basis to license RAL for use in children four weeks of age and older; dosing relevant to this study is as follows:

- 2 through 5 years of age (and at least 10 kg in weight):
  - Chewable tablets: weight based to maximum dose 300 mg, twice daily
- 4 weeks through 2 years of age:
  - If at least 4 weeks of age and weighing 3 kg to less than 25 kg: dose based on weight. Oral suspension can be used for patients weighing 3-20 kg. For patients weighing 11-20 kg, either the chewable tablet or oral suspension can be used.
Considerations for Use of Raltegravir in Neonates

UGT1A1, the enzyme primarily responsible for RAL metabolism, is also the only enzyme that contributes to bilirubin glucuronidation in human hepatocytes, and therefore is essential for the biliary elimination of bilirubin from the body (48). Glucuronidation activity is low in fetuses and in the newborn immediately after birth but increases exponentially over the first weeks and months of life. Hepatic UGT activity in liver samples is very low in samples from second trimester fetuses and increases roughly 10-fold during the third trimester and then another 100-fold during the first three months following a full-term delivery (49). The low level of hepatic UGT activity at birth plays a major role in the elevations of bilirubin routinely seen in the newborn, referred to as physiologic jaundice. In adults, decreased UGT1A1 activity increases plasma concentrations of both bilirubin and RAL. Administration of an exogenous drug that is eliminated by glucurononactone poses special risks in the newborn. A neonatal dosing regimen for such a drug extrapolated from older infants or children may result in accumulation of unexpectedly high and potentially toxic plasma drug concentrations, as has been described for chloramphenicol and ZDV (54). Competition for neonatal albumin binding sites between bilirubin and an exogenous drug may also present a significant risk to the infant, as was seen when administration of sulfisoxazole to low birth weight infants caused kernicterus due to displacement of bilirubin from albumin (60). In vitro evaluation of the effect of RAL on bilirubin-albumin binding was performed in pooled neonatal serum using the peroxidase method (59, 61, 62). RAL had minimal effect on bilirubin-albumin binding at concentrations of 5 and 10 µM, caused a small, but statistically significant, increase in unbound bilirubin at 100 µM and potentially harmful increases at 500 and 1000 µM. The effect of RAL on neonatal bilirubin binding is unlikely to be clinically significant unless concentrations exceed typical peak concentrations of 10 µM (4440 ng/mL) by 50- to 100-fold (63).

IMPAACT P1097 has evaluated washout elimination of RAL in neonates who had received RAL across the placenta from their mothers who were dosed with RAL during pregnancy. In full term infants of normal birth weight, median infant apparent t ½ of RAL was 26.6 (9.3-184) hours, which is prolonged compared to the typical adult terminal elimination (β) t ½ of approximately 7 to 12 hours (21). Enrollment of low birth weight infants (<2500 g) has been completed and preliminary data from low birth weight infants demonstrate a further prolongation of RAL elimination in premature infants.

IMPAACT P1110 has evaluated the safety and pharmacokinetics of RAL when administered to newborn infants at risk of HIV infection. Data from this study served as the basis for FDA and European Medicines Agency approval of RAL for use in full-term neonates at the following doses:

- Birth to 1 Week (once daily dosing using oral suspension based on approximately 1.5 mg/kg/dose)
  - 2 to less than 3 kg: 4 mg once daily
  - 3 to less than 4 kg: 5 mg once daily
  - 4 to less than 5 kg: 7 mg once daily
- 1 to 4 Weeks (twice daily dosing using oral suspension based on approximately 3 mg/kg/dose)
  - 2 to less than 3 kg: 8 mg twice daily
  - 3 to less than 4 kg: 10 mg twice daily
  - 4 to less than 5 kg: 15 mg twice daily
This same dosing will be followed for neonates in P1115; Sections 5.1.1 and 5.1.2 provide further guidance on the timing of dose adjustment aligned with the Step 1 and Step 2 study visit schedules.

Considerations for Use of RAL Chewable Tablets as Dispersible Tablets

Administration of RAL granules for oral suspension requires a complex constitution procedure, including use of single-dose 100 mg packets, mixing cups and syringes, and potable water for each dose. Merck has generated both bio-comparison and modeling data indicating that RAL chewable tablets used in 25 mg dose increments should provide appropriate PK to achieve both efficacy and safety targets across the 3 to 25 kg weight range, and in particular in children weighing less than 10 kg, among whom chewable tablets were not directly evaluated in pediatric development studies. Data indicate that the 25 mg chewable tablet can be used as a dispersible tablet, meeting WHO dispersibility criteria after simple crushing or pre-wetting (followed by stirring and crushing as needed to remove any chunks) in a variety of vehicles. Thus, alternative dosing using chewable tablets as dispersible for infants and children at least four weeks of age and 3-10 kg can be expected to achieve appropriate efficacy and safety. The PK of the chewable tablet formulation have been compared to the granules for suspension formulation in a single-dose study in adults (P068) (29). A uniform pediatric formulation of RAL that is chewable or dispersible will assist with harmonization of antiretroviral formulations, as recommended by the WHO, where dosing guidelines are under final review.

1.9 Rationale for VRC-HIVMAB060-00-AB (VRC01) Dosing

VRC01 is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody that binds to the CD4 binding site of gp120, identified using methods to isolate and screen memory B lymphocytes from the peripheral blood mononuclear cells of HIV-1-infected donors by investigators at the Vaccine Research Center. At 50 mcg/mL, VRC01 neutralizes more than 90% of genetically diverse heterologous strains of HIV-1, and at 1 mcg/mL, more than 70% are neutralized (53). It is not self- or poly-reactive, lacks anti-phospholipid antibody activity (see Investigator’s Brochure), and it does not bind to human adult or fetal tissue. These features suggest that mAb administration will not result in adverse immune phenomena. VRC01 is an IgG1, thereby allowing it to mediate ADCC, a mechanism which may be important to eliminate infected cells (54).

Trials in HIV-seronegative adults

Clinical trials of VRC01 began in 2013 and are ongoing. First-in-human dose escalation studies for safety, tolerability, and PK of IV and SC routes were completed in HIV-1-infected (VRC 601) (49) and HIV-1-uninfected (VRC 602) (55) adults, enrolling 29 and 27 participants, respectively. A clinical trial (HVTN 104) evaluated serial dosing using five different IV or SC regimens of repeated doses of VRC01 administered to 88 healthy, HIV-1-uninfected adults (56). Phase 2b studies of VRC01 for prevention of sexual HIV transmission among uninfected women in sub-Saharan Africa (HVTN 703/HPTN 081) and uninfected men and transgender person who have sex with men (HVTN 704/HPTN 085) are ongoing and have enrolled 1625 and 2459 participants as of June 2018, respectively.

Doses in adult participants have ranged from 1 to 40 mg/kg/dose intravenously and 5 mg/kg/dose subcutaneously given at 2-8 week intervals over durations exceeding 24 months. In HVTN 104, most study participants had either no local reaction or only mild local reactogenicity to infusion or injection. The VRC01 SC administrations were generally associated with mild local reactions during the infusions that included some pruritus (itchiness), redness and swelling, which resolved
within a few minutes to a few hours after the administration was completed. Erythema/induration reactions were reported rarely; the largest diameter for erythema or swelling events that were observed during infusions ranged up to about 9 cm. For 76% of infusions or injections, participants reported no systemic reactogenicity symptoms. When present, most systemic symptoms were mild, with malaise/fatigue, myalgias, and headaches being most common. Of the 3 participants who reported severe systemic reactogenicity symptoms, 2 had concurrent viral infections, and 1 had malaise lasting one day. Adverse events attributed to study product administration on the basis of temporal relationship and other considerations have included AST, ALT and creatinine elevation, decreased neutrophil count, diarrhea, chest discomfort, herpes zoster, generalized rash, and pruritus at the administration site. These laboratory changes and events have resolved and did not require discontinuation of study product administration.

Overall, as of February 22, 2018, VRC01 administration in the dose range from 1 to 40 mg/kg IV and at 5 and 40 mg/kg SC have been assessed as well-tolerated in adults and infants and safe for further evaluation. Cumulatively, across all studies, VRC01 has been administered to over 3500 HIV-uninfected and about 88 HIV-infected adults and about 40 HIV-exposed infants. There have been no serious adverse events assessed as related to VRC01 by the IND Sponsor and no study safety pauses for adverse events.

Trials in HIV-infected adults
There are five studies (RV 398, RV 397, A 5340, A 5342, and 15-I-0140) examining the effect of VRC01 on virologic outcomes among adults with acute or established HIV. Each protocol was designed to address different aspects of the effect of VRC01, including virologic effect when administered during acute HIV infection, effect on the HIV reservoir and effect when administered during an analytical treatment interruption (ATI). All protocols are using a dose of 40 mg/kg/dose, given at 2-4 week intervals for 1-9 doses. As of January 10, 2017, about 80 HIV-1 infected participants have received VRC01 in these studies. Cumulatively across all studies of VRC01, there have been no serious adverse events related to VRC01 that required expedited reporting to the FDA or other regulatory authorities and no study safety pauses for adverse events. The unsolicited adverse events in all studies have been no greater than grade 2 in severity except for an unrelated, grade 3 neutropenia in 15-I-0140. There has been one infusion discontinued for an infusion reaction and one episode of grade 2 urticaria. Protocol 601 demonstrated an antiviral effect of VRC01 when administered as a single drug to viremic adults (49). Protocols A5340 and 15-I-0140 evaluated the antiviral activity of VRC01 when given immediately prior to and during interruption of ART. Study participants were more likely than historical controls to have viral suppression at week 4 (38% vs. 13%, p = 0.04) (26). When used as a single agent during analytical treatment interruption, the delay of viral rebound was greater among participants that lacked pre-existing VRC01 resistant isolates in cell-associated virus.

Trials in HIV-exposed and HIV-infected infants
IMPAACT P1112 is studying the safety and PK of VRC01 administered at birth to newborns born to women with HIV. The first two dose groups received a single dose of 20 mg/kg or 40 mg/kg and have completed follow-up (13 and 14 per group, respectively). A third dose group of 13 breastfed infants has been fully enrolled and is receiving an initial dose of 40 mg/kg at birth and subsequent doses of 20 mg/kg at monthly intervals through six months of age or cessation of breastfeeding. Overall, VRC01 has been well tolerated (48). As of 18 April 2018, there have been no related serious adverse events, no systemic reactions, and no urticarial reactions. Local reactions (erythema, induration, or edema) have been common, occurring in six and 11 infants in the 20 and 40 mg/kg dose groups, respectively. In the third dose group, local reactions occurred in seven infants after the 40 mg/kg initial dose and approximately 20% of infants at each
subsequent 20 mg/kg dose. All local reactions were grade mild or moderate (grade 1-2) and almost all resolved within four hours of injection.

IMPAACT 2008 will study four sequential doses of 40 mg/kg of VRC01, with the first dose given within 14 days of initiating combination antiretroviral therapy, in HIV-infected infants aged 0-12 weeks; this study opened in May 2018.

PK of VRC01
The PK parameters of passively administered VRC01 have been evaluated in HIV-infected and healthy uninfected adults in the VRC 601 and VRC 602 studies, respectively. At 28 days after second administration at 20 mg/kg and 40 mg/kg IV, mean VRC01 serum levels were 55.9±16.8 and 88.9±40.4 mcg/mL in uninfected adults, and were 46.0±26.7 and 64.9±56.7 mcg/mL in HIV-infected adults, respectively. The time to maximum concentration (Tmax) is about 1-3 hours after IV administration and about 1-3 days after SC administration. For the uninfected and infected participants, the terminal half-life was 15±3.9 and 12±4.5 days for IV dosing and 17±2.9 and 11±5 days for SC dosing, respectively. PK parameters determined in IMPAACT P1112 are available for the HIV-exposed infants receiving single doses of VRC01 at 20 mg/kg/dose and 40 mg/kg/dose given subcutaneously. Mean (SD) day 28 levels were 39.3 (14.9) mcg/mL and 75.2 (21.4) mcg/mL for the 20 and 40 mg/kg doses, respectively. For the 20 mg/kg/dose group, the estimated serum half-life was 19.7 (5) days. Peak levels occurred median of 2 and 1 days for the 20 and 40 mg doses (48).

The regimen of 40 mg/kg dose at 0, 2, 6, and 10 weeks selected for the current study is based on PK modeling using data from VRC 601 and 602 and P1112 studies and the dose used in adult studies of VRC01 for antiviral activity. The optimal plasma level of VRC01 required for antiviral activity is yet to be defined in human trials, although viremic adults with low baseline plasma virus concentration have sustained suppression until VRC01 plasma levels dropped to 10 mcg/ml (49). Likewise, the in vivo level of VRC01 to mediate ADCC activity is unknown. Therefore, targeted plasma levels for this study are selected based on the preclinical studies of VRC01 demonstrating that over 91% of viral isolates tested across clades are neutralized at an ID50 of 50 mcg/ml (53). To maintain levels above 50 mcg/ml during the initial weeks of treatment, a second dose will be given two weeks after the first dose. The third and fourth doses will be given at four-week intervals. This regimen is projected to maintain mean VRC01 levels above 50 mcg/ml through the first 16 weeks of life. Subcutaneous dosing is planned, because this route will be feasible in larger trials and will avoid the potential for participants to miss doses due to inability to obtain intravenous access. Subcutaneous dosing also allows this study to build on the safety and PK data obtained from IMPAACT P1112 and IMPAACT 2008, which are using a subcutaneous route.

1.10 Rationale for Formula and Breastfeeding Cohorts and Focus on in utero HIV-infected Infants

Although the first infant described to have achieved remission following initiation of very early therapy (Mississippi Child) was formula fed, and therefore had no ongoing exposure to HIV through breast milk, it is important to study this approach in breastfed infants; the major burden of neonatal infection occurs in resource-constrained settings where breastfeeding is standard of care and critical for child survival. Studying these two cohorts sequentially would delay, by years, findings with implications for the epicenter of perinatal transmission.
While the risk of occurrence of HIV super infection by transmission through breastfeeding is likely low to an infant with in utero HIV infection on ART, this risk still exists while exposure to breast milk continues. It is therefore possible that an in utero HIV-infected infant who received very early therapy and underwent HIV clearance could subsequently become infected through ongoing exposure to breast milk, impacting greatly on the study findings. The possibility of this occurring will be limited by assuring that the infants have ceased breastfeeding for a minimum of six weeks prior to any ARV interruption.

As outlined, this protocol focuses on in utero and not intrapartum infection, but the latter is still a possibility for this cohort. Therefore, these infants should receive the appropriate ARV prophylaxis, based on country-specific guidelines with continued assessment for intrapartum and breast-milk transmission, until infection is excluded. HIV PCR testing will be repeated at 12 weeks to identify any cases of intrapartum or breast-feeding infection prior to exit from the study in whom the enhanced antiviral regimen may impact HIV testing results. Any infants identified as HIV-infected at 12 weeks will be treated based on country guidelines.

1.11 Rationale for Enrolling HIV-Infected Infants Started on ART within 48 Hours of Birth in a Clinical Setting

With widespread coverage of the Mississippi Child, standards of care for high-risk infants are evolving among clinical care providers. In this study, HIV-infected infants who are started on ART within 48 hours of birth in a non-study setting are eligible for enrollment in Cohort 2 within 10 days of birth, at which time the study regimen will be initiated.

All infants diagnosed as in utero HIV-infected outside the study will undergo at least one confirmatory HIV NAT performed at a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory as part of the study. Potential limitations for assessing this ART-started cohort include possibly missing key pre-enrollment data and specimens and differences in ARV dosing prior to enrollment. Eligibility criteria for this cohort are designed to ensure that a minimum set of key pre-enrollment data will be available and case report forms (CRFs) have been designed to collect as much relevant pre-enrollment data as possible. Continued inclusion of this cohort in the study allows comprehensive assessment of infants with in utero HIV infection despite ART use among pregnant women.

1.12 Rationale for Studying Congenital Cytomegalovirus (cCMV)

CMV is an important cause of congenital infection occurring in 1-3% of live births. cCMV infection may lead to sensorineural hearing loss, developmental delay, hematological abnormalities, in particular neutropenia, and may alter cellular immune responses (57-59). Congenital CMV is more prevalent in HIV-infected infants, and HIV-infected infants are more likely to demonstrate symptomatic CMV infection than HIV-exposed uninfected infants. CMV infection may also lead to more rapid progression of HIV infection in co-infected infants. (Kovacs, A. et al 1999) In NICHD/HPTN 040, cCMV was found in 3.5% of the 1,684 infants enrolled. In the HIV-exposed uninfected infants, there were 56 cCMV infections with 15/140 (10.7%) HIV-infected infants having cCMV. The majority of co-infected infants were in utero infected 12/93 (12.9%). Recent analysis also showed that the mothers with CMV viruria had significantly higher rates of perinatal HIV transmission (29.2% vs. 8.1%, p=0.002). They were 5 times (aOR=5.6, 95% CI 1.9-16.8) and nearly 30 times (aOR 29.7, 95% CI 5.4-164.2) more likely to transmit HIV and CMV to their infants, respectively (60). Since HIV and cCMV co-infected infants may also have altered or dysregulated immune responses that may impact on virologic responses to very early treatment, as well as CMV induced neutropenia, in this study, urine
samples will be collected from HIV-infected infants (at entry into Step 2) for CMV testing. It is hypothesized that co-infection with cCMV may influence whether HIV remission will be achieved in the absence of antiviral treatment of CMV infection.

1.13 Rationale for Evaluation of HIV Reservoirs in the Central Nervous System (CNS)

The neurocognitive effects of HIV in perinatal infection is well-established, and major developmental delay is considered an AIDS-defining illness. These effects were more prevalent prior to the availability of ART for children (61) and was a common endpoint in the early clinical trials of ARV use in perinatally-infected children. It is therefore assumed that the majority of HIV-infected infants experience seeding of the CNS during primary infection.

It is known that developmental delay and neurocognitive impairment responds to antivirals, however there is little known on the effect of very early and potent cART on the establishment and persistence of CNS viral reservoirs in perinatal infection (62, 63). Even though these children may achieve undetectable plasma viremia, questions remain about whether virus replication or an inducible reservoir persists in the CNS or if there will be measurable biomarkers of CNS neuroinflammation. Numerous biomarkers have been evaluated in adults with HIV, but little is known in perinatally infected children. Analogous to studies of childhood leukemia and disease-free remission, the potential for CNS reactivation or relapse is an important consideration for long term HIV remission. While incorporation of cerebrospinal fluid (CSF) collection as part of the evaluation of early intensive therapy might be an ideal approach to gain new knowledge on viral dynamics in the CNS, this has potential to negatively impact enrollment into P1115 and may not be logistically feasible as part of routine care. However, some infants enrolled in this study may undergo CSF collection as part of standard of care evaluation for other clinical conditions such as congenital syphilis, sepsis, or tuberculosis. As evaluation of HIV reservoirs in the CNS may be important for assessing the outcome of long term HIV remission, residual CSF (remaining after standard of care collection and evaluation) will be retained for exploratory studies of viral dynamics and identification of inflammatory biomarkers in the CNS.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 To assess HIV remission among neonates with in utero HIV infection who initiate early intensive therapy within 48 hours of birth. HIV remission is defined as having no confirmed plasma HIV-1 RNA ≥ LOD through 48 weeks of ART cessation.

2.2 Secondary Objectives

2.2.1 To assess the safety and tolerability of early intensive therapy regimens in neonates and young infants.

2.2.2 To assess, by regimen (Regimen 1L separately from Regimens 2R+2RV combined), the proportion of infants receiving early intensive therapy who achieve viral suppression (plasma HIV-1 RNA < LOD) at Week 24.

2.2.3 To assess, by regimen (Regimen 1L separately from Regimens 2R+2RV combined), the proportion of infants receiving early intensive therapy who meet virologic and immunologic criteria for treatment cessation.
2.2.4 To assess, by regimen (Regimen 1L separately from Regimens 2R+2RV combined), the relationship between time to achieve confirmed viral suppression (plasma HIV-1 RNA < LOD) and meeting the virologic and immunologic criteria for treatment cessation.

2.2.5 To assess the extent of HIV persistence in infants who achieve HIV remission.

2.2.6 To evaluate immune activation and host and viral determinants, including maternal factors and HIV-specific immune responses, associated with HIV remission.

2.2.7 To assess biomarkers of HIV reservoir size among infants receiving early intensive therapy (including but not limited to proviral HIV DNA load and HIV serostatus).

2.2.8 To assess resistance to ARVs included in the study regimens and to VRC01.

2.2.9 To describe RAL and VRC01 exposures in neonates and young infants.

2.3 Exploratory Objectives

2.3.1 To observe the frequency of intrapartum or early breast milk infection (assessed at approximately 12 weeks of age) following receipt of early intensive therapy.

2.3.2 To explore rates of HIV and cytomegalovirus co-infection in neonates at high risk of perinatal HIV infection.

3.0 STUDY DESIGN

This is a Phase I/II proof of concept exploratory study investigating the hypothesis that early intensive therapy provided to neonates with in utero HIV infection may permit long-term control of HIV replication off ART and lead to HIV remission. The study will also assess the safety and PK of agents provided as part of early intensive therapy.

3.1 Study Regimens

Three early intensive therapy regimens will be assessed:

- **Regimen 1L**, LPV-containing regimen initiated under protocol Version 1.0:
  2 NRTIs + NVP + LPV/r

- **Regimen 2R**, RAL-containing regimen initiated under protocol Version 2.0:
  2 NRTIs + NVP + RAL

- **Regimen 2RV**, RAL- and VRC01-containing regimen initiated under protocol Version 2.0:
  2 NRTIs + NVP + RAL + VRC01

See Section 3.2 for cohort assignment to each regimen and Section 5.0 for detailed information on each regimen.
3.2 Study Cohorts

Infants and their mothers will be enrolled in one of two study cohorts:

- **Cohort 1**: Infants at high risk for *in utero* HIV infection; defined as having been born to a mother with presumed or confirmed HIV infection who did not receive any ARVs during pregnancy; enrolled with their mothers within 48 hours of birth.

- **Cohort 2**: *In utero* HIV-infected, ART-started infants; defined as having at least one positive HIV NAT from a sample collected within 48 hours of birth outside the study and having initiated a qualifying ART regimen within 48 hours of birth outside the study; enrolled with their mothers within 10 days of birth.

Mothers and infants will be enrolled in pairs. Mothers must be willing and able to enroll in the study with their infants and will remain in follow-up for as long as their infants remain in follow-up. However, if mothers withdraw from follow-up after completing study entry procedures, their infants may remain in follow-up.

See Sections Evaluation and Initial Treatment of High-Risk Infants (Step 1) and Management of Infants with Confirmed *in utero* HIV Infection (Step 2) for more information on confirmation of *in utero* HIV infection and subsequent management of mother-infant pairs enrolled in each cohort.

3.2.1 Cohort Accrual Targets by Regimen

**Regimen 1L** (2 NRTIs + NVP + LPV/r) will be evaluated among infants enrolled under protocol Version 1.0. Among 440 mother-infant pairs enrolled in Cohort 1 under protocol Version 1.0, 34 infants with *in utero* HIV infection were identified. An additional 20 mother-infant pairs were enrolled in Cohort 2 under protocol Version 1.0. As such, a total of 54 infants with *in utero* HIV infection received this regimen under protocol Version 1.0. Infants remaining in follow-up when protocol Version 2.0 is implemented will continue to receive this regimen under protocol Version 2.0.

**Regimen 2R** (2 NRTIs + NVP + RAL) and **Regimen 2RV** (2 NRTIs + NVP + RAL + VRC01) will be evaluated among infants enrolled under protocol Version 2.0. Approximately 430 mother-infant pairs will be enrolled in Cohort 1 to identify at least 30 infants with *in utero* HIV infection receiving these two regimens. An additional 15 mother-infant pairs enrolled in Cohort 2 will receive Regimen 2R. Cohort 2 infants will not receive Regimen 2RV.

3.2.2 Accrual Plan by Regimen

Accrual of infants receiving **Regimen 1L** (2 NRTIs + NVP + LPV/r) was completed under protocol Version 1.0. At each site, once all required approvals of protocol Version 2.0 are obtained, follow-up of infants enrolled under protocol Version 1.0 will continue under protocol Version 2.0.

Under protocol Version 2.0, infants receiving **Regimen 2R** (2 NRTIs + NVP + RAL) and infants receiving **Regimen 2RV** (2 NRTIs + NVP + RAL + VRC01) will be enrolled approximately concurrently. All study sites will be potentially eligible to enroll infants receiving Regimen 2R; only selected sites will be eligible to enroll infants receiving Regimen 2RV, based on regulatory and pharmacy considerations for VRC01 as well as operational considerations for the study. Sites
will be assigned to Regimen 2R or Regimen 2RV in an effort to achieve approximately equal
distribution of infants receiving each regimen. Site assignments to each regimen may be changed
over time, but at no time will any site be enrolling infants receiving Regimen 2R and Regimen
2RV concurrently.

3.3 Study Steps

The study consists of four steps:

• Step 1: Evaluation and Initial Treatment of High-Risk Infants

Cohort 1 infants will be enrolled in Step 1 for evaluation of HIV infection and initiation of
early intensive therapy within 48 hours of birth. Infants in whom in utero HIV infection is
excluded will switch from the study regimen to standard perinatal prophylaxis per local
guidelines within two weeks; these infants will continue in Step 1 safety monitoring for an
additional two weeks, undergo final HIV testing at approximately 12 weeks of age, and then
exit the study. Infants in whom in utero HIV infection is confirmed will enter Step 2 at least
two weeks after enrollment in Step 1.

• Step 2: Management of Infants with Confirmed in utero HIV Infection

Cohort 1 infants identified in Step 1 with in utero HIV infection will transition to Step 2 as
described above. Cohort 2 infants will be enrolled directly into Step 2. In Step 2, infants from
both cohorts will receive the study regimen for up to 192 weeks. Beginning at Step 2 Week
84, children who achieved HIV RNA suppression by Week 24, and maintained suppression
thereafter, with no HIV RNA detected at or after Week 48, will be evaluated for possible
treatment cessation.

• Step 3: Treatment Cessation

Children in Step 2 who meet criteria for treatment cessation will enter Step 3 and stop ART.
Children in Step 3 will undergo frequent HIV RNA testing to monitor for viral rebound for as
long as they remain in remission, up to five years from the date of entry into Step 3.

• Step 4: Treatment Re-Initiation

Children who experience viral rebound in Step 3 will enter Step 4 and re-start ART. Children
in Step 4 will undergo frequent HIV RNA testing to monitor their response to ART re-
initiation, until five years of age or six months after viral re-suppression on ART, whichever
is later.

See Section 4.0 for the eligibility criteria associated with each step and to Section 6.3 for
management plans associated with each step.

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.

The eligibility criteria for entry into Step 3 include obtaining informed consent from the child’s parent/guardian. See Section 6.3.2.4 for more information on this informed consent process.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Maternal Inclusion Criteria

4.1.1 Cohort 1 and Cohort 2

4.1.1.1 Mothers will be eligible to enroll with EITHER:

1) **Presumed HIV infection** defined as ≥ one positive rapid HIV antibody test obtained in the peripartum period. Maternal infection must be confirmed, with confirmatory results available within 10 business days of enrollment (see below).

OR

2) **Confirmed HIV infection** defined as positive results from two samples collected at different time points. All samples tested must be whole blood, serum or plasma.

*Sample #1* may be tested using any of the following:
- Two rapid antibody tests from two different manufacturers or based on different principles and epitopes
- One enzyme immunoassay (EIA) OR Western Blot (WB) OR immunofluorescence assay OR chemiluminescence assay
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

*Sample #2* may be tested using any of the following:
- Rapid antibody test for a total of 3 different rapid tests. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved, and all three rapid tests must be from different manufacturers or based on different principles or epitopes.
- One EIA OR WB OR immunofluorescence assay OR chemiluminescence assay
- One qualitative HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
• One total HIV nucleic acid test

All samples tested must be whole blood, serum, or plasma. If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory setting that operates according to Good Clinical Laboratory Practice (GCLP) guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory. For tests performed in other settings, adequate source documentation including the date of specimen collection, date of testing, test performed, and test result must be available. FDA-approved testing methods should be used when possible. If FDA-approved methods are not available, test methods should be verified according to GCLP and approved by the IMPAACT Laboratory Center.

Mothers who enroll in the study with presumed infection (only one positive rapid HIV antibody test obtained in the peripartum period) must have confirmatory testing (see Samples #1 and #2 above) with results available within 10 business days of enrollment. If maternal HIV infection is not confirmed within 10 business days of enrollment, mothers and their infants will be removed from the study. If the mother’s two positive tests were performed in non-certified laboratories, a third confirmatory HIV test must be performed in a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory. The infant will be allowed to remain on study until these results are available.

4.1.1.2 Willing and able to provide written informed consent for participation of herself and her infant (Step 1 and/or Step 2 as applicable). The mother must be of an age to provide legal informed consent as defined by the country in which she resides. If not, informed consent must be obtained from a legal guardian.

4.1.2 Cohort 1 Only

4.1.2.1 Infant eligible and enrolled in Cohort 1

4.1.2.2 No receipt of ARVs during the current pregnancy

*Note: Maternal receipt of ARVs prior to the current pregnancy (including NVP) or during labor and/or the intrapartum period (within five days prior to delivery) of the current pregnancy is permissible.*

4.1.3 Cohort 2 Only

4.1.3.1 Infant eligible and enrolled in Cohort 2

*Note: Maternal receipt of ARVs during the current pregnancy and/or the intrapartum period for the current pregnancy is permissible.*

4.2 Infant Inclusion Criteria, Step 1, Evaluation and Initial Treatment of High-Risk Infants

4.2.1. ≤ 48 hours of age
4.2.2  ≥ 36 weeks gestational age at birth (assessment of gestational age will be based on the best clinical estimate determined by date of last menstrual period, antenatal ultrasound, fundal height, or Ballard Score)

4.2.3  ≥ 2 kg at birth

4.2.4  Mother with presumed or confirmed HIV infection per Section 4.1.1.1

4.2.5  Mother did not receive ARVs during the current pregnancy per Section 4.1.2.2 No receipt of ARVs during the current pregnancy

4.2.6  Able to take ARVs by mouth, nasogastric tube, or gastrostomy tube

4.3 Infant Inclusion Criteria, Step 2. Management of Infants with Confirmed in utero HIV Infection

4.3.1  Able to take ARVs by mouth, nasogastric tube, or gastrostomy tube.

4.3.2  Cohort 1 Only

4.3.2.1  Must have been enrolled in Step 1

4.3.2.2  Confirmed in utero HIV infection (see Section Evaluation and Initial Treatment of High-Risk Infants (Step 1))

4.3.3  Cohort 2 Only

4.3.3.1  ≤ 10 days of age

4.3.3.2  ≥ 36 weeks gestational age at birth (assessment of gestational age will be based on the best clinical estimate determined by date of last menstrual period, antenatal ultrasound, fundal height, or Ballard Score)

4.3.3.3  ≥ 2 kg at birth

4.3.3.4  Mother with presumed or confirmed HIV infection per Section 4.1.1.1

4.3.3.5  At least one NAT positive for HIV infection on a sample drawn within 48 hours of birth

4.3.3.6  Received first dose of ART within 48 hours of birth on a regimen including 2 NRTIs and at least one other agent (e.g., NVP, RAL, LPV/r)

• Dosing of each agent in the regimen should be based on current dosing guidelines (WHO or individual country or local standard guidelines)
• NVP dosing must be at least equivalent to current country or local standard dosing guidelines for prophylaxis
• The FDA recommends avoiding LPV/r in infants < 14 days of age or < 42 weeks postmenstrual age
4.3.3.7 ART regimen (described in 4.3.3.6) was taken daily from date of initiation until study entry

- Other than the exception in the next bullet point for NVP, each agent in the regimen must be taken daily from the date of initiation
- NVP should ideally be taken daily from the date of initiation and must be taken on at least two of the first five days of life (i.e., it is acceptable for NVP to not be taken on up to three of the first five days of life)

4.4 Infant Inclusion Criteria, Step 3, Treatment Cessation

*Note: The criteria in this section may be modified in response to expert panel review.*

4.4.1 Must have been enrolled in Step 2.

4.4.2 Must have reached Step 2 Week 96.

4.4.3 Must have the following based on testing at the local CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory:

4.4.3.1 No confirmed plasma HIV RNA $\geq 200$ copies/mL at Step 2 Week 24 and up to but excluding Step 2 Week 48 (see Section and Cohort 2 ARV Management for procedural guidance related to this criterion)

AND

4.4.3.2 No plasma HIV RNA detected at Step 2 Week 48 and thereafter

*Note: Sample dilution for HIV RNA assays should not occur at or after Step 2 Week 24. In the event that an adequate sample volume cannot be collected at a given study visit, the infant should return to the clinic on a different day within the allowable visit window for a repeat specimen collection attempt. If the repeat attempt is unsuccessful, or if for any reason sample dilution is unavoidable, the infant may be considered for entry into Step 3 as long as dilution occurs only once at or after Step 2 Week 24 and the HIV RNA assays immediately preceding and immediately following the diluted assay are not performed with a diluted sample and provide results that otherwise meet criteria for entry into Step 3.*

4.4.4 If breastfed, must have permanently ceased breastfeeding, with no exposure to breast milk for at least six weeks prior to specimen collection for the testing specified in criterion 4.4.5.

4.4.5 Must have met ALL of the following additional criteria while in Step 2, obtained at $\geq$ Step 2 Week 84 and $\leq$ Step 2 Week 192:

4.4.5.1 Two consecutive negative HIV antibody tests by fourth generation ELISA (performed in the study’s designated central laboratory) at least 8 weeks apart
4.4.5.2 Two consecutive HIV DNA tests with no DNA detected in at least 850,000 PBMCs assayed (performed in the study’s designated central laboratory) at least 8 weeks apart

*Note: One million PBMCs should ideally be assayed; to accommodate variable specimen volumes and cell counts, however, a minimum of 850,000 PBMCs assayed is acceptable.*

4.4.5.3 No plasma HIV RNA detected at the time of the second consecutive negative HIV DNA test (based on testing performed in the study’s designated VQA-certified central laboratory)

4.4.5.4 CD4 cell percentage ≥ 25 AND CD4 cell absolute count ≥ the lower limit of normal for age (i.e., 1000 cells/mL if 2-3 years of age, ≥ 750 cells/mL if 3-4 years of age)

4.4.5.5 Infant assessed by the site investigator or designee as expected to comply with the Step 3 Schedule of Evaluations

4.4.5.6 Mother (or legal guardian if applicable) willing and able to provide written informed consent for child’s participation in Step 3 and Step 4

4.4.6 No plasma HIV RNA detected by testing performed at the local CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory, after criteria 4.4.5.1-4.4.5.5 have been confirmed, with specimen collection for the assay within 14 days prior to Step 3 Entry.

4.5 Infant Inclusion Criteria, Step 4, Treatment Re-Initiation

4.5.1 Must have been enrolled in Step 3.

4.5.2 Plasma HIV RNA ≥ LOD based on by standard quantitative testing performed at the local CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory after ART cessation (see Section 6.3.2.3 for procedural guidance related to this criterion).

*Note: Regardless of HIV RNA test results, any child enrolled in Step 3 may re-initiate ART at the request of his or her parent or guardian; any such child is eligible for inclusion in Step 4.*

4.6 Infant Exclusion Criteria, Step 1 and Step 2

Any clinically significant diseases (other than HIV infection) or clinically significant findings during review of medical history or physical examination prior to entry that, in the investigator’s opinion, would interfere with study participation or interpretation.

4.7 Concomitant Medications Requiring Pre-Approval

For infants receiving LPV/r, the following medications should not be prescribed due to potential drug interactions with LPV/r; site investigators should provide immediate clinical management of infants for whom these medications may be indicated while contacting the Clinical Management
Committee (CMC) as soon as possible and within two business days for approval of longer term management:

- Anti-infectives: ketoconazole, systemic corticosteroids, ergot derivatives, systemic itraconazole (topical steroids do not require pre-approval).
- Antihistamines: terfenadine, loratadine, astemizole
- Sedative Hypnotics: alprazolam, clorazapam, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem
- Anticonvulsants, except lamotrigine, gabapentin, and levetiracetam
- Analgesic Narcotics: meperidine, propoxyphene, alfentanil, fentanyl, methadone, hydrocodone, oxycodone, and tramadol
- Analgesic/non-steroidal: piroxicam
- Antiarrhythmics: amiodarone, encainide, flecainide, propafenone, quinidine, lidocaine, disopyramide, and mexiletine
- Antibiotics: systemic erythromycin, clarithromycin
- Anticoagulants: warfarin
- Tricyclics: amitriptyline, clomipramine, desipramine, imipramine, mapprotline, nortriptyline, and trimipramine
- SSRIs and non-tricyclics: bupropion, nefazodone, sertraline, fluoxetine, paroxetine, trazodone, and venlafaxine
- Antiemetics: cisapride, dronabinol, and ondansetron
- Beta-blockers: metoprolol, pentobutolol, pindolol, and timolol
- Calcium channel blockers: bepridil, amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, diltiadpine, ditradipine, and verapamil
- Hypolipemics
- Immunosuppressants: cyclosporine, tacrolimus
- Neuroleptics: clozapine, pimozide, chlorpromazine, clorazepate
- Stimulants: dextroamphetamine, methamphetamine
- Cancer chemotherapy: tamoxifen, etoposide, paclitaxel, vinblastine, and vincristine
- St. John’swort
- Synthetic corticosteroids: fluticasone, budesonide
- Alpha-blockers: alfuzosin

For infants receiving RAL, the following should not be co-administered; site investigators should provide immediate clinical management of infants for whom these medications may be indicated while contacting the CMC as soon as possible and within two business days for approval of longer term management:

- Rifampin
- Phenobarbital
- Phenytin

For any infants requiring rifampin-containing tuberculosis treatment, contact the CMC to discuss ARV regimen management.

4.8 Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and informed consent forms (ICFs) approved by their IRBs/ECs and any
other applicable regulatory entities (REs). A Site Implementation Plan (SIP) will be required from each site participating in the study. The SIP must be submitted to the Protocol Team for review and approval before protocol registration can occur.

Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific ICFs WILL be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files. Upon receiving final IRB/EC and any other applicable RE approvals for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which is available on the RSC website at:
https://rsc.tech-res.com/clinical-research-sites/protocol-registration/policy-manual

Enrollment of maternal and infant participants will be done through the Subject Enrollment System on the Data Management Center website (at https://www.fstrf.org).

4.9 Co-enrollment Procedures

Co-enrollment in other research protocols will require the approval of the protocol co-chairs of P1115 and the other research protocol.

5.0 STUDY TREATMENT

5.1 Study Regimens, Administration, and Duration

As detailed below, study regimens will be comprised of different combinations of NRTIs, NVP, LPV/r, RAL, and VRC01. For RAL and VRC01, weight-based dosing tables are provided in the study-specific MOP. NRTIs will be chosen by the site investigator and dosed according to WHO or individual country or local standard guidelines. For reference, US and WHO guidelines are available at:

https://aidsinfo.nih.gov/guidelines
http://www.who.int/hiv/pub/guidelines/en/

All products included in all regimens must be provided by prescription from an authorized prescriber. Site pharmacists must receive new prescriptions from an authorized prescriber if dose
adjustments are required based on body weight or body surface area in participants who outgrow their dose and are switched to the next dosing increment. New prescriptions must also be received for all formulation changes (e.g., changes from liquid to tablet formulations).

5.1.1 Step 1 Regimens

The Step 1 regimen should be initiated as soon as possible after enrollment and should not be deferred pending collection of specimens for HIV testing or the availability of HIV test results. The first dose of each ARV in the Step 1 regimens should be administered within 48 hours of birth. For infants receiving Regimen 2RV, VRC01 should also be administered within 48 hours of birth; however, if this is not possible, VRC01 may be administered within 72 hours of birth.

The Step 1 regimen should be discontinued (switch to standard perinatal prophylaxis) when test results are available to exclude in utero HIV infection. This switch may occur at the Step 1 Week 1 visit if test results are available at that visit; otherwise, the switch must occur no later than the date of the Step 1 Week 2 visit. For infants with confirmed in utero HIV infection, the study regimen will be continued in Step 2.

5.1.1.1 Regimen 1L: 2 NRTIs + NVP (received in Step 1 under protocol Version 1.0)

Note: Infants enrolled in Cohort 1/Step 1 under protocol Version 1.0 received this regimen in Step 1. This regimen is listed here for completeness but will not be provided in Step 1 under protocol Version 2.0.

2 NRTIs chosen by the site investigator and dosed according to WHO or individual country or local standard guidelines

PLUS NVP:
- For infants < 37 weeks gestational age at birth: 4 mg/kg per dose orally twice daily until the Step 1 Week 1 visit, then 6 mg/kg per dose orally twice daily
- For infants ≥ 37 weeks gestational age at birth: 6 mg/kg per dose orally twice daily

5.1.1.2 Regimen 2R: 2 NRTIs + NVP + RAL

Note: All study sites are potentially eligible to enroll infants in Cohort 1/Step 1 receiving this regimen under protocol Version 2.0.

2 NRTIs chosen by the site investigator and dosed according to WHO or individual country or local standard guidelines

PLUS NVP:
- For infants < 37 weeks gestational age at birth: 4 mg/kg per dose orally twice daily until the Step 1 Week 1 visit, then 6 mg/kg per dose orally twice daily
- For infants ≥ 37 weeks gestational age at birth: 6 mg/kg per dose orally twice daily

PLUS RAL:
- 1.5 mg/kg orally once daily from the Step 1 Entry visit until the Step 1 Week 1 visit
- 3 mg/kg orally twice daily from the Step 1 Week 1 visit until the Step 1 Week 2 visit
5.1.1.3 Regimen 2RV: 2 NRTIs + NVP + RAL + VRC01

Note: Only selected sites are eligible to enroll infants in Cohort 1/Step 1 receiving this regimen, based on regulatory and pharmacy considerations for VRC01 as well as operational considerations for the study. Sites will be assigned to Regimen 2R or Regimen 2RV in an effort to achieve approximately equal distribution of infants receiving each regimen. Site assignments to each regimen may be changed over time but at no time will a site be enrolling infants receiving Regimen 2R and Regimen 2RV concurrently.

2 NRTIs chosen by the site investigator and dosed according to WHO or individual country or local standard guidelines

PLUS NVP:
- For infants < 37 weeks gestational age at birth: 4 mg/kg per dose orally twice daily until the Step 1 Week 1 visit, then 6 mg/kg per dose orally twice daily
- For infants ≥ 37 weeks gestational age at birth: 6 mg/kg per dose orally twice daily

PLUS RAL:
- 1.5 mg/kg orally once daily from the Step 1 Entry visit until the Step 1 Week 1 visit
- 3 mg/kg orally twice daily from the Step 1 Week 1 visit until the Step 1 Week 2 visit

PLUS VRC01
- 40 mg/kg subcutaneously once at the Step 1 Entry visit

5.1.2 Step 2 Regimens

The Step 2 regimen should be initiated at entry into Step 2 and may be continued until Step 2 Week 192. The regimen will include four ARVs until 12 weeks after two consecutive HIV RNA levels < LOD, at which time NVP will be discontinued. Thereafter, the regimen will include three ARVs and will be continued until entry into Step 3 or until the infant comes off study.

5.1.2.1 Regimen 1L: 2 NRTIs + NVP + LPV/r (infants enrolled under Version 1.0 only)

Note: All infants receiving this regimen in Step 2 under protocol Version 2.0 were previously enrolled in Cohort 1 or Cohort 2 under protocol Version 1.0 and initiated this regimen under protocol Version 1.0. For these infants, use of this regimen will continue under protocol Version 2.0. These infants will not switch to Regimen 2R or Regimen 2RV under protocol Version 2.0.

2 NRTIs chosen by the site investigator and dosed according to WHO or individual country or local standard guidelines

PLUS NVP:
- 6 mg/kg per dose orally twice daily from Step 2 Entry until the Step 2 Week 4 visit
- 200 mg/m² orally twice daily OR WHO weight band dosing starting at the Step 2 Week 4 visit
PLUS LPV/r:
- LPV 300 mg/m² + RTV 75 mg/m² orally twice daily (as LPV/r) initiated at ≥ 14 days of age AND ≥ 42 weeks postmenstrual age

Note: Postmenstrual age is calculated by adding postnatal age to gestational age at birth as determined using methods described in Sections 4.2.2 ≥ 36 weeks gestational age at birth (assessment of gestational age will be based on the best clinical estimate determined by date of last menstrual period, antenatal ultrasound, fundal height, or Ballard Score) and 4.3.3.2.

5.1.2.2 Regimen 2R: 2 NRTIs + NVP + RAL

Note: All study sites are potentially eligible to enroll infants receiving this regimen under protocol Version 2.0. This regimen will be provided in Step 2 to infants enrolled in Cohort 1 and Cohort 2 under protocol Version 2.0.

2 NRTIs chosen by the site investigator and dosed according to WHO or individual country or local standard guidelines

PLUS NVP:
- 6 mg/kg per dose orally twice daily from Step 2 Entry until the Step 2 Week 4 visit
- 200 mg/m² orally twice daily OR WHO weight band dosing starting at the Step 2 Week 4 visit

PLUS RAL:
- Cohort 1:
  - 3 mg/kg orally twice daily from Step 2 Entry until the Step 2 Week 2 visit
  - 6 mg/kg orally twice daily starting at the Step 2 Week 2 visit
- Cohort 2 infants less than 5 days of age at entry into Step 2:
  - 1.5 mg/kg orally once daily until the Step 2 Week 1 visit (schedule the Step 2 Week 1 visit as close to 7 days of age as possible)
  - 3 mg/kg orally twice daily from the Step 2 Week 1 visit until the Step 2 Week 4 visit (schedule the Step 2 Week 4 visit as close to 28 days of age as possible)
  - 6 mg/kg orally twice daily starting at the Step 2 Week 4 visit
- Cohort 2 infants 5-10 days of age at entry into Step 2:
  - 3 mg/kg orally twice daily from the Step 2 Week 1 visit until the Step 2 Week 4 visit (schedule the Step 2 Week 4 visit as close to 28 days of age as possible)
  - 6 mg/kg orally twice daily starting at the Step 2 Week 4 visit

5.1.2.3 Regimen 2RV: 2 NRTIs + NVP + RAL + VRC01

Note: This regimen will be provided in Step 2 to infants enrolled in Cohort 1 under protocol Version 2.0 at selected sites (this regimen will not be provided to infants in Cohort 2). Only selected sites are eligible to enroll infants receiving this regimen, based on regulatory and pharmacy considerations for VRC01 as well as operational considerations for the study. Sites will be assigned to Regimen 2R or Regimen 2RV in an effort to achieve approximately equal distribution of infants receiving each regimen. Site assignments to each regimen may be changed over time but at no time will a site be enrolling infants receiving Regimen 2R and Regimen 2RV concurrently.
2 NRTIs chosen by the site investigator and dosed according to WHO or individual country or local standard guidelines

PLUS NVP:
- 6 mg/kg per dose orally twice daily from Step 2 Entry until the Step 2 Week 4 visit
- 200 mg/m² orally twice daily OR WHO weight band dosing starting at the Step 2 Week 4 visit
PLUS RAL:
- 3 mg/kg orally twice daily from Step 2 Entry until the Step 2 Week 2 visit
- 6 mg/kg orally twice daily starting at the Step 2 Week 2 visit

PLUS VRC01
- 40 mg/kg subcutaneously at Step 2 Entry, Step 2 Week 4, and Step 2 Week 8

*Note: Prior to entry into Step 2, Cohort 1 infants receiving Regimen 2RV would have received a first dose of VRC01 (40 mg/kg) at Step 1 Entry.*

5.1.3 Step 3

No study treatment will be provided in this step.

5.1.4 Step 4 Regimens

Children who enter Step 4 will re-start the same ART regimen they received in Step 2 prior to ART cessation upon entry into Step 3.

5.1.5 Administration

*Note: The content of this section is limited to study-supplied study agents, i.e., RAL and VRC01. Weight based dosing tables are provided for both products in the study-specific MOP. For RAL, the dosing shown in the weight-based tables is based on approximately 1.5 mg/kg/dose, 3 mg/kg/dose and 6 mg/kg/dose; these approximate doses may be used in place of the exact calculated dose.*

5.1.5.1 RAL

Doses of RAL should be administered orally, with or without food, once daily (Step 1 Entry until Step 1 Week 1) or twice daily (Step 1 Week 1 until Step 1 Week 2 and throughout Step 2). Caregiver instructions for preparing and administering RAL oral granules for suspension and RAL chewable/dispersible tablets are provided in the study-specific MOP. Caregiver competency to properly prepare and administer doses to infants and children should be confirmed and documented by site staff prior to administration of the first dose of each formulation.

5.1.5.2 VRC01

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 3.2 mL, corresponding to infant weights ranging from 2 to 8 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.

5.2 Study product Formulations

5.2.1 RAL Oral Granules

RAL oral granules for suspension may be taken by infants and children up to 20 kg body weight. At 3 kg and four weeks of age it is permissible to switch to the chewable/dispersible tablet formulation.

RAL oral granules are for suspension in water only. After reconstitution the final concentration is 10 mg/mL.

RAL oral granules for suspension will be provided in foil pouches that each contain 100 mg. Store the pouches securely in a dry place at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). See USP Controlled Room Temperature. Do not refrigerate or freeze. The pouches should remain sealed until used.

The oral granules for suspension formulation has a banana flavor and contains the following: raltegravir, hydroxypropylcellulose, ethylcellulose, Opadry I film coat blend, sucralose, monoammonium glycyrrhizinate, natural banana flavor, crospovidone, mannitol, Avicel Cl-611, and magnesium stearate.

5.2.2 RAL Chewable/Dispersible Tablets

RAL oral granules may be taken by infants up to 20 kg body weight. Once a child weighs 3 kg and is four weeks of age, the chewable/dispersible tablet formulation may be taken. At 20 kg body weight children should switch to the tablet formulation.

The chewable/dispersible tablets may be chewed or swallowed whole or dispersed. For dispersion, the tablets should be crushed and dispersed in water, juice, breast milk, or formula using the following procedures: Dissolve the number of RAL chewable/dispersible tablets required for the infant’s body weight. Up to three of the 25 mg tablets (a total of 75 mg) may be dissolved in approximately 5 mL of water, juice, breast milk, or formula; 100 mg tablets should be dissolved in 10 mL of water, juice, breast milk, or formula. Once the tablet is wetted (after ~2 minutes), crush the tablet while in the liquid with a spoon and stir until dispersed. The full amount of liquid must be administered orally (e.g., directly from the container or with a spoon or syringe) within 30 minutes post-dissolution.

RAL chewable/dispersible tablets will be provided as 100 mg pale orange, oval-shaped, orange-banana flavored tablets scored on both sides and as 25 mg pale yellow, round, orange-banana flavored tablets. Store the tablets in the original package with the bottle tightly closed. Keep the desiccant in the bottle to protect from moisture. Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). See USP Controlled Room Temperature.
RAL chewable/dispersible tablets contain phenylalanine, a component of aspartame. Each 25 mg tablet contains approximately 0.05 mg phenylalanine. Each 100 mg tablet contains approximately 0.10 mg phenylalanine. Phenylalanine can be harmful to patients with phenylketonuria.

Each 100 mg tablet contains 108.6 mg of raltegravir (as potassium salt), equivalent to 100 mg of raltegravir free phenol and the following inactive ingredients: ammonium hydroxide, crospovidone, ethylcellulose 20 cP, fructose hydroxypropyl cellulose, hypromellose 2910/6cP, magnesium stearate, mannitol, medium chain triglycerides, monoammonium glycyrrhizinate, natural and artificial flavors (orange, banana, and masking that contains aspartame), oleic acid, PEG 400, red iron oxide, saccharin sodium, sodium citrate dihydrate, sodium stearyl fumarate, sorbitol, sucralose and yellow iron oxide.

Each 25 mg tablet contains 27.16 mg of raltegravir (as potassium salt), equivalent to 25 mg of raltegravir free phenol and the following inactive ingredients: ammonium hydroxide, crospovidone, ethylcellulose 20 cP, fructose, hydroxypropyl cellulose, hypromellose 2910/6cP, magnesium stearate, mannitol, medium chain triglycerides, monoammonium glycyrrhizinate, natural and artificial flavors (orange, banana, and masking that contains aspartame), oleic acid, PEG 400, saccharin sodium, sodium citrate dihydrate, sodium stearyl fumarate, sorbitol, sucralose and yellow iron oxide.

5.2.3 VRC01

VRC01 will be supplied in 3 mL glass vials. The vials are filled to 2.25 ± 0.1 mL at a concentration of 100 (±10) mg/mL. The vials contain a clear, colorless to yellow liquid essentially free of visible particles; some opaque or translucent particles may be present. The formulation buffer is composed of 25 mM sodium citrate, 50 mM sodium chloride, and 150 mM L-arginine hydrochloride at pH 5.8. The vials are intended for single use only and thus contain no preservative.

The VRC01 product label designates long-term storage at -35°C to -15°C (-31°F to 5°F). At clinical research sites, storage in a qualified, continuously monitored, temperature-controlled freezer with temperature excursions from -45°C to -10°C (-49°F to 14°F) is acceptable.

Following thawing, vials of VRC01 may be stored for up to 24 hours at controlled room temperature (maximum 27°C) and/or up to 4 weeks at 2°C to 8°C. If stored at 2°C to 8°C, vials should be equilibrated to controlled room temperature (maximum 27°C) for a minimum of 30 minutes and may be held at room temperature for up to 8 hours prior to product preparation. The product may not be stored in direct sunlight.

For subcutaneous administration, the required volume of VRC01 will be loaded into a 5 or 10 mL sterile syringe. Preparation must be performed using aseptic technique in a laminar flow biosafety cabinet. Prepared syringes containing VRC01 may be stored at 2°C to 8°C for up to 24 hours or at controlled room temperature (maximum 30°C) for up to 4 hours (unless institutional policies specify shorter expiry timeframes, in which case institutional policies should be followed). The product may not be stored in direct sunlight.

Refer to the study-specific MOP for further information on product storage, thawing, preparation, and stability.
5.3 Product Supply, Acquisition/Distribution, and Accountability

5.3.1 Study Product Supply/Acquisition/Distribution

RAL, and VRC01 will be supplied through the study:

- RAL oral granules for suspension and RAL chewable/dispersible tablets will be supplied by Merck Research Laboratories.
- VRC01 will be supplied by the Vaccine Research Center.

RAL oral granules (with lidded cups and syringes), RAL chewable/dispersible tablets, and VRC01 will be made available to study sites through the NIAID Clinical Research Products Management Center (CRPMC). RMS High-Flo Subcutaneous Safety Needle Sets and 26-gauge needles in both 4 mm and 6 mm lengths will be purchased centrally and made available to sites through the CRPMC. Upon successful completion of protocol registration procedures, the above-listed products may be obtained by the site pharmacist following instructions provided in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

NRTIs, NVP, LPV/r and any other ARVs not listed above will NOT be provided through the study. These ARVs must be provided by prescription and supplied from local non-study sources. 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

Oral dispensers and push-in-bottle adapters (PIBAs) in limited sizes are available from the CRPMC for use with the non-study-supplied ARVs (3 ml and 5 ml oral dispensers; 22 mm and 33 mm PIBAs).

5.3.2 Study Product Accountability

Site pharmacists must maintain complete records of all study product supplies and needle sets received from the CRPMC. The product lot number associated with each dose of VRC01 administered will be recorded in participant study records and on CRFs.

Partially used vials of VRC01 are not permitted to be administered to other study participants or used for in vitro experimental studies. Any unused portion of entered vials, any used syringes, and any unused filled syringes should be disposed of in a biohazard container and incinerated or autoclaved per approved local site policy.

At US sites, all unused RAL and VRC01 must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

At non-US sites, the site pharmacist must follow the instructions in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for the destruction of unused RAL and VRC01.
6.0 PARTICIPANT MANAGEMENT

See Section 7.3 for guidance on toxicity grading. Site investigators will manage toxicities based on severity grade and, in some cases, relationship to study regimen, per the management guidelines described below and in Sections 6.1 and 6.2. These guidelines were developed with two aims: (1) to maximize participant safety and (2) to minimize unnecessary interruptions in ART that could undermine the primary aim of the study — to maximally treat HIV infection.

In this study, study agents are administered in three ways that are outside of current guidelines:

- NVP is provided to infants less than 14 days of age using an investigational dose.
- VRC01, an investigational agent, is provided within 72 hours of birth and in the first 12 weeks of age.
- Combination therapy with four ARVs is provided until 12 weeks after confirmation of HIV RNA < LOD.

The study-specific toxicity management guidelines take the above-listed considerations into account in that they address anticipated adverse events assessed as possibly, probably, or definitely related to one or more ARVs or to VRC01, and they apply only while infants are receiving ARVs and/or VRC01 at protocol-specified investigational doses, i.e., through the Step 2 Week 36 visit. Any adverse events that occur after the Step 2 Week 36 visit, or that are assessed as probably not or not related to one or more ARVs or VRC01, should be managed by site investigators consistent with current standards of care for pediatric clinical care and ARV management. Similarly, toxicities assessed as related to concomitant medications (other than ARVs or VRC01) should be managed by site investigators consistent with local standards of care.

Consultation on all aspects of clinical management is available from the CMC at any time (impaaact.p1115cmc@fstrf.org). Consultation with the CMC is required for selected toxicities, as specified in Sections 6.1 and 6.2. For infants receiving VRC01, the CMC should be informed as soon as possible and within two business days of:

- Grade 1 or higher serum sickness
- Grade 1 or higher urticarial or other hypersensitivity reaction
- Grade 3 or higher adverse events assessed as possibly, probably or definitely related to VRC01.

For all infants, the CMC should also be consulted as soon as possible and within two business days on any decision to hold or permanently discontinue any ARV at any time during follow-up, as continuous receipt of suppressive ARV therapy is considered essential for the primary aim of the study.

Noting that anti-tuberculosis medications such as rifampicin, isoniazid and pyrazinamide can cause hepatic, skin and hematologic toxicity, site investigators should also consult the CMC on management of toxicities occurring among infants being co-treated for HIV and tuberculosis. Further operational guidance for consulting in the CMC is provided in the study-specific MOP.
Assessment of adverse event relatedness to a study agent for purposes of clinical management and recording on CRFs is made by the site investigator, based on the following guidelines:

- **Definitely Related**: The adverse event and administration of the study agent are related in time, and a direct association can be demonstrated.

- **Probably Related**: The adverse event and administration of the study agent are reasonably related in time, and the adverse event is more likely explained by the study agent than other causes.

- **Possibly Related**: The adverse event and administration of the study agent are reasonably related in time, and the adverse event can be explained equally well by causes other than the study agent.

- **Probably Not Related**: A potential relationship between the study agent and the adverse event could exist (i.e., the possibility cannot be excluded), but the adverse event is most likely explained by causes other than the study agent.

- **Not Related**: The adverse event is clearly explained by another cause not related to the medication.

*Note: The above classification applies for adverse event documentation (source documentation and CRF completion) and management but does not apply for expedited adverse event (EAE) reporting. EAEs will be reported, per the DAIDS EAE Manual, as related or not related. See Section 7.0 for more information on EAE reporting.*

To minimize ARV interruptions, single suspect ARVs can be held for up to three days while continuing the remainder of the ARV regimen; the CMC should be contacted as soon as possible and within two business days to assist with decisions about holding the entire ARV regimen or permanent discontinuation or substitution of individual ARVs. When any ARV or VRC01 is held for toxicity management, relevant clinical and laboratory evaluations should be repeated per the grade- or toxicity-specific guidance provided below until the toxicity resolves or is stabilized.

It is also important to consider the many other possible causes of clinical abnormalities during evaluation. Immune reconstitution inflammatory syndrome (IRIS), although not yet described in neonates, could be confused with toxicity. Therefore, possible causes such as cytomegalovirus, syphilis, hepatitis B and tuberculosis should be sought, if clinically indicated. Neonatal rashes such as erythema toxicum can be confused with drug-related rashes.

### 6.1 General Toxicity Management Guidelines

The following general guidelines (by grade) apply to management of ARVs and VRC01 in response to toxicities — other than those listed in Section 6.2 — that occur through the Step 2 Week 36 visit and are assessed as possibly, probably, or definitely related to an ARV or VRC01. Management of the toxicities listed in Section 6.2 should be guided by that section. All other management should be pursued by site investigators consistent with current standards of care for pediatric clinical care and ARV management.
Grade 1 Toxicity:
- Continue all ARVs/VRC01.

Grade 2 Toxicity:
- Continue all ARVs/VRC01.

Grade 3 Toxicity:
- Upon initial recognition of a Grade 3 clinical or laboratory toxicity:
  - Site investigator should repeat the laboratory test to confirm the Grade 3 value as soon as possible and generally within two business days of site awareness.
  - Explanations for the toxicity other than ARVs/VRC01 should be considered.
  - If the initial Grade 3 toxicity is assessed as possibly, probably not, or not related to an ARV or VRC01, the entire ARV regimen and VRC01 should be continued.
  - If the initial Grade 3 toxicity is assessed as probably or definitely related to an ARV or VRC01, the suspect agent should be held while awaiting confirmation (other agents should be continued). The CMC should be contacted within two business days.

- If the result of the repeat test is Grade 1 or 2, the relevant management guidelines (Grade 1 or 2) should be followed.

- If the result of the repeat test confirms a Grade 3 toxicity:
  - Explanations for the toxicity other than ARVs/VRC01 should be considered.
  - If the confirmed Grade 3 toxicity is assessed as possibly, probably not, or not related to an ARV or VRC01, all agents should be resumed/continued.
  - If the confirmed Grade 3 toxicity is assessed as probably or definitely related to an ARV or VRC01, the suspect agent should be held, unless the site investigator feels that continuation of the agent is in the participant’s best interest, AND the CMC should be consulted within two business days. The decision about whether to hold all agents or only the suspect agent should be made in consultation with the CMC within two business days. If the site investigator feels that continuation of all agents is in the participant’s best interest, the CMC should be informed.

- Following any confirmed Grade 3 toxicity, the infant should be re-evaluated weekly until improvement to ≤ Grade 2.

- If one or more agents were held due to a confirmed Grade 3 toxicity, these agents may be resumed once the toxicity improves to ≤ Grade 2. Following resumption, if the Grade 3 toxicity recurs (and is confirmed), the suspect agent should be permanently discontinued. If one or more agents are not clearly implicated, the CMC should be consulted prior to permanent discontinuation.

- Infants experiencing Grade 3 toxicities requiring permanent discontinuation of an ARV or VRC01 should be re-evaluated at least weekly until improvement to ≤ Grade 2 or until stabilized and no longer in need of such frequent monitoring, as determined by the site investigator.
Grade 4 Toxicity:

- Upon initial recognition of a Grade 4 clinical or laboratory toxicity:
  - Site investigator should repeat the test to confirm the Grade 4 value within two business days of site awareness. If the test cannot be repeated within two business days, it should be repeated as soon as possible.
  - Explanations for the toxicity other than ARVs/VRC01 should be considered.
  - If the initial Grade 4 toxicity is assessed as probably not or not related to an ARV or VRC01, the entire ARV regimen and VRC01 should be continued.
  - If the initial Grade 4 toxicity is assessed as possibly, probably or definitely related to an ARV or VRC01, the suspect agent should be held while awaiting confirmation (other agents should be continued). The CMC should be contacted within two business days.

- If the result of the repeat test is Grade 1, 2, or 3 the relevant management guidelines (Grade 1, 2, or 3) should be followed.

- If the result of the repeat test confirms a Grade 4 toxicity:
  - Explanations for the toxicity other than ARVs/VRC01 should be considered.
  - If the confirmed Grade 4 toxicity is assessed as probably not or not related to an ARV or VRC01, all agents should be resumed/continued.
  - If the confirmed Grade 4 toxicity is assessed as possibly, probably, or definitely related to an ARV or VRC01, the suspect agent should continue to be held AND the CMC should be consulted within two business on management of all agents. Alternatively, the site investigator may resume the previously held agent if he or she has new and compelling evidence that the toxicity is probably not related or not related to the agent. In this case, consultation with the CMC is required within two business days.

- Following any confirmed Grade 4 toxicity, the infant should be re-evaluated weekly until improvement to ≤ Grade 2.

- Once a Grade 4 toxicity that was assessed as possibly, probably, or definitely related to an ARV or VRC01 improves to ≤ Grade 2, four-drug ARV treatment and VRC01 may be resumed. In these cases, alternative ARVs should replace suspect ARVs, if possible. Alternatively, if the Grade 4 toxicity is subsequently assessed as probably not or not related to an ARV or VRC01, the original regimen may be resumed at the discretion of the site investigator, with approval in advance from the CMC.

- Infants experiencing Grade 4 toxicities requiring permanent discontinuation of an ARV or VRC01 should be re-evaluated at least weekly until improvement to ≤ Grade 2 or until stabilized and no longer in need of such frequent monitoring, as determined by the site investigator.

6.2 Special Toxicity Management Guidelines

The text and tables in this section were developed to address selected toxicities that are most common and with which NVP, RAL, and/or VRC01 are associated. These guidelines apply to management of the selected toxicities through the Step 2 Week 36 visit. As noted in each section, the recommendations generally apply to toxicities assessed as possibly, probably, or definitely related to an ARV or to VRC01. All other management should be pursued by site investigators consistent with current standards of care for pediatric clinical care and ARV management.
Certain toxicities are more like to be associated with ARVs than with VRC01; for those, the text and tables in this section focus on ARV management. However, should any toxicity be assessed as probably not or not related to one or more ARVs, VRC01 should be considered as a possible cause; consult the CMC with any questions.

6.2.1 Anemia and Neutropenia

Hematologic toxicity is common among infants with HIV and receiving ARVs, particularly during the first months of life. Interpretation of abnormal values and management of ARVs is particularly challenging in the context of international clinical trials because there are distinct ethnic and geographic differences in the normal ranges of hematologic parameters (64-66). Therefore, a normal value in some settings could be classified as toxic per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), and potentially lead to inappropriate medication changes. In this context, it is noted that whereas laboratory values will be graded per the DAIDS AE Grading Table, to ensure uniformity across sites, decisions to modify ARV regimens will be deferred to the site investigator’s assessment of whether the hematologic changes are abnormal and assessed as possibly, probably, or definitely related to ARV use.

Guidelines for anemia and neutropenia are as follows:

<table>
<thead>
<tr>
<th>CONDITION AND SEVERITY</th>
<th>ARV MANAGEMENT</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2</td>
<td>Continue all ARVs</td>
<td>None</td>
</tr>
<tr>
<td>Grade 3 possibly related</td>
<td>Continue all ARVs</td>
<td>Repeat test to confirm within 3 business days. Continue suspect ARV while awaiting result. If repeat assessment is ≤ Grade 2, manage as per Grade 1 or 2. If repeat assessment is Grade 3 or 4, hold suspect ARV and consult with the CMC within 2 business days about ARV changes.</td>
</tr>
<tr>
<td>Grade 3 probably or definitely related OR Grade 4 possibly, probably, or definitely related</td>
<td>Hold suspect ARV</td>
<td>Repeat test within 3 business days to confirm. If repeat assessment is ≤ Grade 2, manage as per Grade 1 or 2. If repeat assessment is Grade 3 or 4, hold suspect ARV and consult with the CMC within 2 business days about ARV changes.</td>
</tr>
</tbody>
</table>
ZDV, trimethoprim/sulfamethoxazole (TS), and NVP are associated with anemia and/or neutropenia. It can be difficult to ascertain which is the most likely cause of toxicity. Generally, ZDV is considered more likely than NVP to cause anemia, and TS more likely than NVP to cause neutropenia. The final decision on stopping or substituting a medication is up to the site investigator, but the CMC should be consulted about any ARV changes. Acute changes in ARV management that the investigator deems critical to participant care need not wait for CMC approval. If TS is given for pneumocystis carinii pneumonia (PCP) prophylaxis, and the site investigator considers TS as a possible or probable cause of ≥ Grade 3 hematologic toxicity, an alternate PCP prophylaxis regimen may be substituted while ART continues (at the discretion of the investigator) and abnormal laboratory value(s) are followed weekly. If ≥ Grade 3 toxicity persists for ≥ 21 days, despite discontinuing TS, ZDV should be discontinued and substituted with another ARV. If toxicity resolves to ≤ Grade 2 within 21 days, resume/continue ARVs and continue routine monitoring.

6.2.2 Rash

Of the ARVs included in the study regimens, NVP is the most likely to be associated with rash, both in isolation and as part of a systemic hypersensitivity reaction. The Supplemental Toxicity Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis Adverse Events in APPENDIX III must be used for grading rash toxicities.

See Sections 6.2.6 and 6.2.7 for management of injection site reactions and urticarial or other hypersensitivity reactions that may be associated with administration of VRC01.

<table>
<thead>
<tr>
<th>CONDITION AND SEVERITY</th>
<th>ARV MANAGEMENT</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2A</td>
<td>Continue all ARVs</td>
<td>Monitor rash closely</td>
</tr>
<tr>
<td>Grade 2B</td>
<td>If on NVP: hold NVP if considered possibly, probably, or definitely related and continue other ARVs.</td>
<td>Test ALT within 3 business days and evaluate for symptoms of clinical hepatitis and hypersensitivity reaction. Hold NVP while awaiting result; continue other ARVs.</td>
</tr>
<tr>
<td></td>
<td>If any clinical symptoms of hepatitis or ALT elevation or hypersensitivity reaction, permanently discontinue NVP and consult with CMC on study regimen.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If the rash is not generalized or if there is a definitive explanation for the rash (e.g., varicella), NVP may be continued with no additional evaluation required.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If not on NVP: continue all ARVs.</td>
<td>Rash may be treated symptomatically but should be monitored closely by the site investigator.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Hold suspect ARV if possibly, probably, or definitely related.</td>
<td>If there is no definitive explanation for the rash (e.g., varicella), test ALT and, if elevated, manage per the Hepatic Toxicity table in Section 6.2.3.</td>
</tr>
<tr>
<td></td>
<td>If on NVP, discontinue immediately and consult with CMC for recommendations.</td>
<td></td>
</tr>
<tr>
<td>CONDITION AND SEVERITY</td>
<td>ARV MANAGEMENT</td>
<td>FOLLOW-UP</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Grade 4</td>
<td>If on NVP, discontinue immediately and consult with CMC for recommendations. If not on NVP, hold suspect ARV if possibly, probably, or definitely related.</td>
<td>Test ALT and consult the CMC on ARV management.</td>
</tr>
</tbody>
</table>

### 6.2.3 Hepatic Toxicity

<table>
<thead>
<tr>
<th>CONDITION AND SEVERITY</th>
<th>ARV MANAGEMENT</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2 Asymptomatic</td>
<td>Continue all ARVs during evaluation (including NVP).</td>
<td>Repeat test as soon as possible and within 14 days. If repeat assessment is Grade 2, continue ARVs and continue to monitor every 14 days until resolves. If infant becomes symptomatic, follow guidance for symptomatic hepatitis.</td>
</tr>
<tr>
<td>CONDITION AND SEVERITY</td>
<td>ARV MANAGEMENT</td>
<td>FOLLOW-UP</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Grade 3 Asymptomatic</td>
<td>Continue all ARVs (including suspect ARVs) during evaluation</td>
<td>Repeat test within 3 business days and assess for alternative cause. If repeat assessment is ≤ Grade 2, manage as per Grade 1 or 2. If repeat assessment is Grade 3 and is attributed to an alternative cause (e.g. concomitant illness or medication [probably not or not related to ARVs]), all ARVs may be continued at the discretion of the site investigator. Treat the underlying illness or remove the likely causative agent. If the repeat assessment is Grade 3 and is assessed as possibly, probably, or definitely related to one or more ARVs, hold suspect ARV. Repeat testing weekly. Once the toxicity grade is ≤ Grade 2, if the site investigator wishes to resume the suspect ARV, consultation with the CMC is required in advance. If a suspect ARV is resumed following a hold, repeat testing should be performed one week after resumption. If the result of this testing is Grade 3 or 4, consult the CMC. If infant becomes symptomatic, follow guidance for symptomatic hepatitis.</td>
</tr>
<tr>
<td>Grade 4 Asymptomatic</td>
<td>If on NVP: Hold NVP, do not wait for laboratory confirmation. If not on NVP: consider holding other potentially associated ARV until confirmed and consult with CMC.</td>
<td>Repeat test within 3 business days, in addition to total bilirubin and INR, if available at the site, and assess for alternative cause. If repeat assessment is &lt; Grade 4, manage per the grade of the repeat assessment. If repeat assessment is Grade 4, hold suspect ARV. Consult the CMC on ARV regimen and frequency of repeat assessments while following ALT/AST at least weekly. If the toxicity is assessed as probably or definitely related to suspect ARV, permanently discontinue the suspect ARV. If infant becomes symptomatic, follow guidance for symptomatic hepatitis.</td>
</tr>
</tbody>
</table>
SYMPTOMATIC HEPATITIS
possibly, probably, or definitely related to an ARV

<table>
<thead>
<tr>
<th>CONDITION AND SEVERITY</th>
<th>ARV MANAGEMENT</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs and symptoms of hepatitis include but are not limited to fatigue, malaise, anorexia, nausea, acholic stools, bilirubinuria, jaundice, liver tenderness, and/or hepatomegaly</td>
<td>If on NVP: can continue or hold NVP based on degree of clinical suspicion for hepatitis. If not on NVP: continue all other ARVs until evaluated.</td>
<td>Immediately perform AST and ALT tests, as well as total bilirubin and INR (if available). If AST or ALT is Grade 3 or 4, immediately hold NVP (if receiving) but can continue other ARVs during evaluation. Consult the CMC on ARV regimen and frequency of repeat assessments (in general, at least weekly re-assessment is recommended). If it is determined that the infant has clinical hepatitis and suspect ARV cannot be excluded as the cause, suspect ARV should be permanently discontinued.</td>
</tr>
</tbody>
</table>

6.2.4 Hyperbilirubinemia

Due to the potential for RAL to affect bilirubin elimination, total bilirubin concentrations will be monitored through the first four weeks of infant life. Any observed hyperbilirubinemia will be graded for severity and managed by site investigators according to local standards of care, including use of interventions to lower bilirubin levels such as phototherapy and exchange transfusion. Bilirubin levels and any such interventions will be recorded on CRFs.

With respect to ARV regimen management, in the event of any total bilirubin concentration >16.0 mg/dL, RAL will be held until the concentration is ≤16.0 mg/dL. Infants who receive phototherapy may continue to receive RAL as long as the total bilirubin concentration is ≤16.0 mg/dL.

6.2.5 Reactogenicity Monitoring for Infants Receiving VRC01

6.2.5.1 Reactogenicity Monitoring for Infants Receiving VRC01

Site clinicians will monitor infants for reactogenicity on each day of administration of VRC01:

- 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 (timed from the infusion end time), 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 (timed from the infusion end time), 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. At Step 1 Entry, 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 (timed from the infusion end time).

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 recorded on CRFs. 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.

6.2.5.2 Monitoring by Infant Caregivers

The mothers or other caregivers of infants receiving VRC01 in Step 1 or Step 2 will be instructed to complete memory aid documents to record infant signs and symptoms for seven days following each administration of VRC01, beginning on the day of administration. The memory aids will capture mothers’ assessments of local injection site reactions (redness, warmth, swelling, tenderness) and systemic signs and symptoms (temperature, rash, swelling of joints, vomiting, diarrhea, alertness, feeding, sleeping, irritability). Mothers will also be instructed to contact study staff if any grade 1 or higher signs or symptoms are identified. If grade 1 or higher signs or symptoms are reported, mothers will be instructed to return to the study clinic with their infants as soon as possible (within 48 hours) for further evaluation.

For infants receiving multiple doses of VRC01 in Step 2, three days after visits at which VRC01 is administered, mothers (or caregivers) will be contacted by study staff to report their reactogenicity assessments by telephone. In-person or home visits may also be substituted for telephone contacts if preferred by study staff or mothers. Seven days after each visit, an in-person visit will be conducted. The allowable window for the three-day contacts is -1 to +3 days; the allowable window for the seven-day visits is ±3 days. During the three-day contacts and seven-day visits, study 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 and CRFs.
### 6.2.6 Injection Site Reactions

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>VRC01 MANAGEMENT</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2</td>
<td>Continue administration of VRC01 doses. Use alternate injection site until event resolves to less than Grade 1</td>
<td>Evaluate at subsequent visits per SoE.</td>
</tr>
</tbody>
</table>
| Grade 3, resolves within two hours | Defer VRC01 until event reviewed with CMC. | Contact CMC within 2 business days.  
  • If CMC and site investigator agree, may administer subsequent VRC01 dose. |
| Grade 3, persists longer than two hours | Defer VRC01 until event reviewed with CMC. | Contact CMC within 2 business days.  
  • Provide immediate clinical management per site investigator and subsequently in consultation with CMC.  
  • If no alternative etiology is identified, permanently discontinue VRC01.  
  • If alternative etiology identified and CMC agrees, may administer subsequent VRC01 dose. If grade 3 injection site reaction recurs, permanently discontinue VRC01. |
| Grade 4 | Permanently discontinue VRC01. | Contact CMC within 2 business days.  
  • Provide immediate clinical management per site investigator and subsequently in consultation with CMC. |
### 6.2.7 Urticaria or Other Hypersensitivity Reaction

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>VRC01 MANAGEMENT</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
</table>
| Grade 1, 2, 3, 4 | Stop VRC01 administration. Defer VRC01 until event reviewed with the CMC. | • Contact CMC within 2 business days.  
• Assess for alternative cause; treat the underlying illness or remove the likely causative agent.  
• Provide immediate clinical management per site investigator (see study-specific MOP for guidance) and subsequently in consultation with CMC.  
• If diagnosis confirmed and assessed by either site investigator or CMC as related to VRC01, permanently discontinue VRC01.  
• If diagnosis not confirmed or definite alternative cause identified and event has resolved and CMC agrees, may administer subsequent VRC01 dose. If event recurs, permanently discontinue VRC01. |

### 6.2.8 Serum Sickness

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>VRC01 MANAGEMENT</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
</table>
| Grade 1 | Defer VRC01 until event reviewed with CMC. | • Contact CMC within 2 business days.  
• Assess for alternative cause; treat the underlying illness or remove the likely causative agent.  
• Provide immediate clinical management per site investigator and subsequently in consultation with CMC.  
• If diagnosis confirmed and assessed by either site investigator or CMC as related to VRC01, permanently discontinue VRC01.  
• If diagnosis not confirmed or possible alternative cause identified and event has resolved and CMC agrees, may administer subsequent VRC01 dose. If event recurs at any grade, permanently discontinue VRC01. |
**SERUM SICKNESS**

*characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea*

possibly, probably, or definitely related to VRC01

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>VRC01 MANAGEMENT</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
</table>
| Grade 2  | Defer VRC01 until event reviewed with CMC. | • Contact CMC within 2 business days.  
• Assess for alternative cause.  
• Provide immediate clinical management per site investigator and subsequently in consultation with CMC.  
• If diagnosis confirmed and assessed by site investigator or CMC as related to VRC01, permanently discontinue VRC01.  
• If diagnosis not confirmed or probable alternative cause identified and event has resolved and CMC agrees, may administer subsequent VRC01 dose. If event recurs at any grade, permanently discontinue VRC01. |
| Grade 3 or 4 | Defer VRC01 until event reviewed with CMC. | • Contact CMC within 2 business days.  
• Assess for alternative cause.  
• Provide immediate clinical management per site investigator and subsequently in consultation with CMC.  
• If diagnosis confirmed and assessed by site investigator or CMC as related to VRC01, permanently discontinue VRC01.  
• If diagnosis not confirmed or definite alternative cause identified and event has resolved and CMC agrees, may administer subsequent VRC01 dose. If event recurs at any grade, permanently discontinue VRC01. |
### 6.2.9 Elevated Creatinine

**ELEVATED CREATININE**  
possibly, probably, or definitely related to VRC01

<table>
<thead>
<tr>
<th>SEVERITY</th>
<th>VRC01 MANAGEMENT</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2</td>
<td>Continue administration of VRC01 doses.</td>
<td>• Evaluate at subsequent visits per SoE or more frequently at the discretion of site investigator.</td>
</tr>
</tbody>
</table>
| Grade 3 | Defer VRC01 until event reviewed with CMC. | • Contact CMC within 2 business days.  
• Repeat test within 3 working days.  
• If repeat test result is ≤ Grade 2, manage as per Grade 2.  
• Assess for alternative cause; treat the underlying illness or remove the likely causative agent.  
• If possible alternative cause identified and event has resolved to <Grade 3 and CMC agrees, may administer subsequent VRC01 dose. If event recurs at Grade 3 or higher, permanently discontinue VRC01.  
• If no possible alternative cause identified, permanently discontinue VRC01. |
| Grade 4 | Defer VRC01 until event reviewed with CMC. | • Contact CMC within 2 business days.  
• Repeat test within 3 working days.  
• If repeat test result is ≤ Grade 2, manage as per Grade 2.  
• Assess for alternative cause; treat the underlying illness or remove the likely causative agent.  
• If probable alternative cause identified and event has resolved to <Grade 3 and CMC agrees, may administer the next VRC01 dose. If event recurs at Grade 3 or higher, permanently discontinue VRC01.  
• If no probable alternative cause identified, permanently discontinue VRC01. |
6.3 Participant Management Plan

6.3.1 Evaluation and Initial Treatment of High-Risk Infants (Step 1)

See APPENDIX II-A.

Infants in Cohort 1 will empirically start early intensive therapy per Section 5.1.1 within 48 hours of birth and undergo evaluation for HIV infection as outlined below.

Enrollment must occur with sufficient time available to initiate the study regimen within 48 hours of birth. The first dose of each ARV in the regimen should be administered within 48 hours of birth. For infants receiving Regimen 2RV, VRC01 should also be administered within 48 hours of birth; however, if this is not possible, VRC01 may be administered within 72 hours of birth. When necessary, the Step 1 Entry visit may be conducted as a split visit, with most required procedures performed on the day of enrollment and administration of VRC01 and other associated procedures (e.g., reactogenicity evaluations) performed the next day.

Two samples for HIV NAT should also be collected, at least one hour apart, within 48 hours of birth; however, if the second sample cannot be collected within 48 hours of birth, it may be collected thereafter, within 12 hours after the first sample (the first sample must be collected within 48 hours of birth). Results of both tests must be available by Step 1 Week 2. HIV DNA PCR, quantitative and qualitative HIV RNA PCR, and HIV TNA PCR are acceptable, and one of the two tests must be a quantitative HIV RNA PCR; the second test can also be a quantitative HIV RNA PCR, but an HIV DNA PCR or an HIV TNA PCR is desirable. At least one of the tests must be performed at a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory. Any residual samples (whole blood, plasma, cell pellets, other) should be stored for additional testing if needed.

If the two tests provide discordant results, the CMC should be consulted for guidance on additional testing to be performed. Additional test results should be available as soon as possible and within 10 business days, and infants should generally remain on the study regimen pending receipt of the additional results; however, the CMC will provide infant management guidance on a case-by-case basis.

- **Infants with *in utero* HIV infection**

  Infants with two positive HIV NATs, with at least one sample collected within 48 hours of birth and one positive test performed in a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory, will meet diagnostic criteria for *in utero* HIV infection and enter Step 2 after completing two weeks of follow-up in Step 1 (i.e., at the time of the Step 1 Week 2 visit).

- **Infants without *in utero* HIV infection**

  Infants who do not meet diagnostic criteria for *in utero* HIV infection as described above will discontinue the study regimen and switch to standard perinatal prophylaxis per local guidelines. This switch may occur at the Step 1 Week 1 visit if test results are available to exclude *in utero* infection at that visit; otherwise, the switch must occur no later than the date of the Step 1 Week 2 visit. These infants will continue to be monitored for safety through the Step 1 Week 4 visit, undergo a final HIV NAT at the Step 1 Week 12 visit, and then exit the study (with referral to standard of care services per local guidelines).
6.3.2 Management of Infants with Confirmed *in utero* HIV Infection (Step 2)

See **APPENDIX II-B**.

6.3.2.1 Cohort 1

Cohort 1 infants with confirmed *in utero* HIV infection will enter Step 2 and continue the study regimen in Step 2.

6.3.2.2 Cohort 2

Infants in Cohort 2 will have had ART initiated within 48 hours of birth outside the study. Upon enrollment in the study (into Step 2), the study regimen will be initiated per Section 5.1.2.

Infants may be enrolled in Cohort 2 with a single positive HIV NAT from a sample collected within 48 hours of birth (outside the study) but must have infection confirmed by a second positive HIV NAT within 10 business days of enrollment. The confirmatory test may be an HIV DNA PCR, a quantitative or qualitative HIV RNA PCR, or an HIV TNA PCR. At least one test must be performed in a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory. If the mother or infant is receiving ARVs, an HIV DNA PCR or an HIV TNA PCR may be more sensitive. If the second test does not confirm the initial positive result, the CMC should be notified, and a third specimen should be collected for a third test (selected in consultation with the CMC), with the result available within 10 additional business days. The infant should remain on study, and on the study regimen, until the third result is available and the infant’s HIV status is confirmed in consultation with the CMC. If the second and third tests are negative, the first test will be presumed to have been false-positive. If infection is not confirmed, the infant will exit the study (with referral to standard of care services per local guidelines).

6.3.2.3 Cohort 1 and Cohort 2 ARV Management

See **APPENDICES APPENDIX II-B and APPENDIX II-C**.

Infants in both Cohort 1 and Cohort 2 will receive a four-ARV regimen in Step 2 until 12 weeks after they have two consecutive HIV RNA levels < LOD, at which time (≥ 12 weeks after the specimen collection date for the second consecutive test), NVP will be discontinued (unless an alternate regimen including NVP is selected in consultation with the CMC). Thereafter, a three-ARV regimen will be continued.

In cases of ARV intolerance or toxicity, infants may discontinue the offending ARV(s) while remaining on a combination of at least three ARVs expected to sustain suppression of HIV replication. ARVs may similarly be discontinued in response to presumed or confirmed antiretroviral resistance. All such ARV changes should be made in consultation with the CMC.

Serial plasma HIV RNA testing will be performed at Step 2 Weeks 2, 4, 9, 12, 16, 20, and 24, and then every 12 weeks thereafter. Serial CD4 count testing will be performed approximately every 12 weeks.
Infants with confirmed HIV RNA ≥200 copies/mL at Step 2 Week 24 and up to but excluding Step 2 Week 48 will NOT be eligible for treatment cessation. Any single HIV RNA value ≥200 copies/mL at Week 24 or up to but excluding Week 48 must be repeated within three weeks (specimen collection for the confirmatory test must occur within three weeks of specimen collection for the initial test). If the confirmatory test confirms the initial result, or if specimen collection for the confirmatory test cannot be completed within three weeks, the infant will be considered ineligible for treatment cessation. If the confirmatory test result is < 200 copies/mL, the infant will remain potentially eligible for treatment cessation.

See Section Evaluation to Determine Eligibility for Treatment Cessation for information on virologic monitoring and management beginning at Step 2 Week 48.

6.3.2.4 Evaluation to Determine Eligibility for Treatment Cessation

See APPENDIX II-C.

Infants in Step 2 who do not achieve the plasma HIV RNA requirements in Section Must have the following based on testing at the local CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory: will remain in Step 2 for 192 weeks and then exit the study, with referral to standard of care treatment per local standard guidelines. For these infants, the Step 2 Week 192 visit will serve as the final study visit.

Infants in Step 2 do who achieve the plasma HIV RNA requirements in Section Must have the following based on testing at the local CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory: will undergo further evaluation for possible treatment cessation in Step 3, beginning at Step 2 Week 84. Children will be eligible to enter Step 3 and undergo treatment cessation when they have met ALL of the eligibility criteria in Section 4.4. See APPENDIX II-C and the Laboratory Processing Chart (LPC) for specific instructions on handling of laboratory assays to screen for Step 3 eligibility.

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.

Children who do not initially meet all criteria for treatment cessation will continue in Step 2 on ART and undergo rescreening at 12-week intervals. Children not meeting all
criteria by Week 192 will exit the study (with referral to standard of care treatment per local guidelines).

6.3.3 Treatment Cessation (Step 3)

See APPENDIX II-D.

Upon entry into Step 3, ART will be stopped and the child will be monitored with HIV RNA testing at Weeks 1, 2, 3, 4, 6, and 8, and every four weeks thereafter. To minimize turnaround time, testing will first be performed using an on-demand assay. If this testing yields a positive result, an additional specimen will be collected as soon as possible and within 72 hours for a standard quantitative HIV RNA assay performed at the local CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory. The standard quantitative HIV RNA assay should be performed such that results are available as soon as possible and within 96 hours of specimen collection (any residual samples should be stored for additional testing if needed). Clinical management will be based on the results of standard quantitative HIV RNA assays. Children who maintain HIV RNA < LOD will remain in Step 3 and will have additional testing for evidence of HIV persistence. Children with HIV RNA ≥ LOD will enter Step 4 and re-start ART.

6.3.4 ART Re-Initiation (Step 4)

See APPENDIX II-E.

Children will re-initiate ART at entry into Step 4 and be monitored with plasma HIV RNA testing every two weeks through Step 2 Week 12, then every 12 weeks thereafter. Children whose HIV RNA is not re-suppressed to < LOD by Step 4 Week 12 will have genotypic resistance testing performed if the RNA level is > 1000 copies/mL at the previous visit; if resistance is identified, the ART regimen may be changed in consultation with the CMC. Children will continue to be followed in Step 4 through five years of age or until six months after viral re-suppression on ART, whichever is later.

6.3.5 Management of Infants Co-infected with Tuberculosis

If a child on study develops tuberculosis, the site investigator may change the ART regimen, with approval and input from the CMC, to allow co-administration of rifampin. The child will remain on study and will be eligible for treatment cessation as long as the criteria in Section 4.4 are met and tuberculosis treatment is completed.

6.3.6 Management of Infants Who Undergo Lumbar Puncture for Clinical Care

Lumbar punctures will not be performed for this study. However, for any HIV-infected infant who undergoes lumbar puncture for clinical care during follow-up, any residual CSF should ideally be stored for study purposes. Infants’ mothers (or legal guardians) will be asked to provide optional informed consent for this; consent may be declined with no impact on other aspects of infant study participation. Refer to the LPC for instructions on storing CSF.

6.3.7 Management of Mothers of Enrolled Infants

Mothers of infants who are HIV exposed but uninfected (Cohort 1) will be followed until their infants complete the Step 1 Week 12 visit.
Mothers of infants with confirmed *in utero* HIV infection (Cohort 1 and Cohort 2) will be followed for as long as their infants remain on study.

Mothers will provide demographic information and health history, a blood sample for HIV RNA, and stored samples for HIV sequencing and immune studies (HLA typing, host genetic factors). Sequencing of maternal and infant HIV will be conducted to further confirm mother-child HIV transmission and assess full-length HIV genomes for intact HIV. Interval maternal histories will be collected every six months including health status and current ARVs; clinical reports of maternal HIV RNA levels and CD4 counts will be collected if available.

If HIV-infected infants’ mothers become unavailable after enrollment (e.g., have expired or moved away), infants may remain on study as long as the legal guardian provides consent for continued infant study participation (see also Section 10.1).

### 6.3.8 Laboratory Evaluations

#### 6.3.8.1 Pharmacokinetics

Plasma will be collected and stored for population analyses of RAL and VRC01 exposures (there will be no individual dose adjustments for RAL or VRC01).

#### 6.3.8.2 Safety Laboratory Evaluations

Hematology (complete blood count with differential) and chemistries will be used to monitor for toxicity per APPENDICES APPENDIX II-A to APPENDIX II-E.

#### 6.3.8.3 Studies of Viral Suppression and Persistence

Ultrasensitive methods to quantify HIV reservoirs will be carried out at regular intervals per APPENDICES II-C.

Immunologic correlates of HIV-1 suppression and persistence will also be studied. HIV-1 specific antibodies will be evaluated using ELISA and Western blot. HIV-specific CD4+ and CD8+ T cell responses will be measured by intracellular cytokine (IL-2, IFN-g) assays. The percentage of peripheral blood CD8+ T cells that co-express CD38 and DR will be measured using flow cytometry. These studies will be carried out at defined time points as outlined in APPENDICES II-B to APPENDIX II-E.

See APPENDICES I, Maternal Schedule of Evaluations and APPENDICES II-A to APPENDIX II-E. Infant Schedules of Evaluations, for a complete description of the clinical and laboratory evaluations, and the LPC for complete laboratory procedures to be performed.

### 6.4 Premature Discontinuation from Study Follow-up

Infants who prematurely discontinue from study follow-up will complete Premature Discontinuation visits per the relevant Schedule of Evaluations (APPENDICES II-B to APPENDIX II-E as appropriate).
6.4.1 Infants will be discontinued from the study for the following reasons:

- HIV infection is not confirmed in the mother.
- *In utero* HIV infection is not confirmed in the infant.
- The infant does not meet criteria for treatment cessation by Week 192.
- The infant is not able to attend study visits as required by the study.
- The infant is lost to follow up.
- The mother (or legal guardian if applicable) withdraws consent.
- The investigator determines that further participation would be detrimental to the infant’s health or well-being.

6.4.2 Mothers will be discontinued from the study for the following reasons:

- HIV infection is not confirmed in the mother.
- *In utero* HIV infection is not confirmed in the infant.
- The infant is discontinued from follow-up per other criteria in Section Infants will be discontinued from the study for the following reasons:
- The mother is not able to attend study visits as required by the study.
- The mother is lost to follow up.
- The mother withdraws consent.
- The investigator determines that further participation would be detrimental to the mother’s health or well-being.

If the mother discontinues study follow-up, the infant will still continue follow-up if the infant is still able to attend study visits as required by the study and consent has not been withdrawn.

7.0 EXPEDITED ADVERSE EVENT (EAE) REPORTING

7.1 EAE Reporting to DAIDS


The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at: http://rsc.tech-res.com/clinical-research-sites/safety-reporting/dais/paper-eae-reporting.

For questions about DAERS, contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, contact the DAIDS RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com.
7.2 EAE Reporting Requirements for this Study

- The SAE (Serious Adverse Event) Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study for the period of time defined in Section 7.4. Subsequently, the SUSAR (Suspected Unexpected Serious Adverse Reaction) Reporting Category will be used.

- Other medically-significant events for which expedited reporting is required include:
  - Grade 3 or 4 rash/cutaneous toxicity
  - Grade 4 asymptomatic hepatic toxicity
  - Grade 3 or 4 symptomatic hepatic toxicity
  - Grade 3 or higher serum sickness
  - Grade 3 or higher urticarial or other hypersensitivity reactions
  - Grade 4 injection site reactions
  - All malignancies
  - All IRIS events

- The study agents for which expedited reporting is required are: nevirapine, lopinavir/ritonavir, raltegravir, and VRC01.

7.3 Grading Severity of Events

Adverse events will be graded according to the DAIDS AE Grading Table, Corrected Version 2.1, dated July 2017, which is available on the RSC website: http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables

Exceptions to the above apply to cutaneous/skin rash/dermatitis adverse events, which will be graded according to APPENDIX III, and axillary measured fever and injection site pain/tenderness, which will be graded as follows:

**Axillary Measured Fever**

- Grade 1  37.4 to < 38.0°C (99.3 to < 100.4°F)
- Grade 2  38.0 to < 38.7°C (100.4 to < 101.7°F)
- Grade 3  38.7 to < 39.4°C (101.7 to < 102.9°F)
- Grade 4  ≥ 39.4°C (≥ 102.9°F)

**Injection Site Pain/Tenderness**

- Grade 1  Mild reaction to light touch with no or minimal limitation of movement of limb
- Grade 2  Persistent crying (up to one hour) with no or light touch, or significant limitation of movement of limb
- Grade 3  Persistent crying for more than one hour or interference with ability to sleep or eat
- Grade 4  Inconsolable crying for more than two hours
7.4 EAE Reporting Period

- The EAE reporting period at the SAE Reporting Category for this study encompasses the time when an infant may be receiving the investigational dose of NVP, combination therapy with four ARVs, and/or VRC01.
  
  - In Step 1, this is operationalized as the period from Step 1 Entry through the Week 4 visit.
  
  - In Step 2, this is operationalized as the period from Step 2 Entry through the Week 36 visit.

This reporting period also applies to the other medically significant events for which expedited reporting is required (as listed in Section 7.2).

- The EAE reporting period at the SUSAR Reporting Category for this study includes the time from the end of SAE reporting period until the end of study participation for each infant.

- After the above-specified periods, only SUSARs will be reported if study staff become aware of such events on a passive basis (e.g., from publicly available information).

Every effort will be made by study staff to provide appropriate care and counseling to the infant or referral to appropriate resources for the safety of the infant as needed. Any unanticipated problems will be reported to the DAIDS Medical Officer at the same time as the problems are reported to the responsible site IRB/EC overseeing the research according to pre-established procedures as required by 45 CFR 46.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design

This is a multi-center, Phase I/II proof of concept exploratory study to assess HIV remission after treatment cessation in HIV-infected children who initiated early intensive therapy within 48 hours of birth. Infants are enrolled in either Cohort 1 or Cohort 2:

- **Cohort 1**: Infants at high risk for *in utero* HIV infection; defined as having been born to a mother with presumed or confirmed HIV infection who did not receive any ARVs during pregnancy; enrolled within 48 hours of birth into Step 1.

- **Cohort 2**: *In utero* HIV-infected, ART-started infants; defined as having at least one positive HIV NAT from a sample collected within 48 hours of birth outside the study and having initiated a qualifying ART regimen within 48 hours of birth outside the study; enrolled within 10 days of birth into Step 2.

Infants in Cohort 1 will initiate the study regimen within 48 hours of birth. Infants with negative HIV test results from the specimens drawn within 48 hours of birth will discontinue the study regimen and switch to perinatal ARV prophylaxis per country or local standard guidelines when their test results become available (expected no later than the Step 1 Week 2 visit). Infants without *in utero* HIV-infection will be monitored for safety in Step 1 for four weeks, undergo
final HIV testing at approximately 12 weeks of age, and then exit the study. In utero HIV-infected Step 1 infants will enroll in Step 2. HIV-infected infants will be followed for up to 192 weeks in Step 2. Children who are eligible for ART cessation and enter Step 3 will be followed in Step 3 for as long as they remain in remission, up to 5 years from the date of entry into Step 3. If viral rebound occurs in Step 3, children will enter Step 4 and be followed in Step 4 through five years of age or until six months after viral re-suppression on ART, whichever is later. Infants’ mothers at entry will have HIV RNA level measured and will have blood samples stored for future studies. HIV-infected infant’s mothers will be followed at six-month intervals to update their health status, viral load, and ARV information.

In utero HIV-infected infants in Cohort 1 are the primary focus for assessing early intensive therapy for HIV remission. Under protocol Version 1.0, among 440 Cohort 1 infants receiving Regimen 1L (2 NRTIs + NVP + LPV/r), 34 (7.7%) were identified as in utero HIV-infected. Under Protocol Version 2.0, an additional 430 Cohort 1 infants receiving Regimen 2R (2 NRTIs + NVP + RAL) or Regimen 2RV (2 NRTIs + NVP + RAL + VRC01) and up to 15 Cohort 2 infants receiving regimen 2R (2 NRTIs + NVP + RAL) will be enrolled to identify 45 in utero HIV-infected infants.

HIV-infected children who meet criteria for treatment cessation will enter Step 3 and stop ART; children who do not meet these criteria by Step 2 Week 192 will exit the study as specified in Sections 6.3.2.4 and 6.4.1. HIV-infected children who stop ART and who do not have viral rebound for ≥ 12 weeks after ART cessation will have additional testing done to assess HIV persistence. Children with viral rebound after ART cessation will enter Step 4 and re-initiate ART and will be monitored for virologic response.

Infants will either breastfeed or be formula fed. Data will be analyzed separately for infants receiving Regimen 1R (initiated under protocol Version 1.0) and infants receiving Regimen 2R or 2RV (initiated under protocol Version 2.0), and also by cohort, but will be combined across feeding method. Additional analyses will summarize data by feeding method.

Limitations

Limitations for assessing ART-started children in Cohort 2 include potential selection bias (e.g., since these infants may enroll up to 10 days after birth and after starting ARVs), possible lack of key early measurements and specimens, and potential heterogeneity with respect to antepartum maternal ART.

The Version 2.0 regimens are not randomized which would avoid systematic differences across regimens and, because sites will be assigned to Regimen 2R or Regimen 2RV, regimens may be confounded with site. Any comparisons between regimens will need to be carefully interpreted.

Secondary analyses are specified within numerous subgroups and it is understood that sample sizes in these groups will be smaller, and thus estimation will lose precision.

The infant-feeding method groups may be confounded with the site of enrollment because sites are expected to have pre-dominant infant feeding methods.
8.2 Outcome Measures

8.2.1 Primary

8.2.1.1 HIV remission, defined as no confirmed HIV RNA ≥ LOD through 48 weeks of ART cessation.

*Note: If the Week 48 sample is missing, use the next available sample (first available after the Week 48 visit window).*

8.2.2 Secondary

8.2.2.1 Grade 3 or higher adverse events possibly, probably or definitely related to any component of the study regimen. These outcomes will be based on data collected through CRFs. Relatedness will be based on reports from the site with adjudication by the CMC.

8.2.2.2 Viral suppression to consistent HIV-1 RNA < LOD through week 24.

8.2.2.3 Meeting all eligibility criteria for ART cessation as defined in Section 4.4.

8.2.2.4 Meeting the selected eligibility criteria for ART cessation defined in Sections 4.4.5.1-4.4.5.4 among infants who also met the viral suppression criteria for ART cessation in Section Must have the following based on testing at the local CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory:

8.2.2.5 The following outcomes among children who discontinue ART and do not rebound within 12 weeks of discontinuation which will be based on stored samples:

8.2.2.6 HIV persistence as measured by plasma viremia (single copy), droplet digital DNA, replication competent HIV reservoirs.

8.2.2.7 Immune activation markers (%CD8+/DR+ T cells) and HIV-specific immune responses: HIV-specific antibodies and HIV-specific T cell responses.

8.2.2.8 RAL and VRC01 concentrations among treated neonates and young infants (see Section 9.0 for more detail).

8.3 Randomization and Stratification

This is not a randomized study. Four cohorts of infants will be defined based on cohort of enrollment and infant feeding intent at time of enrollment (breastfed or formula fed):

- Cohort 1A: formula fed high risk
- Cohort 1B: breastfed high risk
- Cohort 2A: formula fed HIV-infected, ART-started
- Cohort 2B: breastfed HIV-infected, ART-started
8.4 Sample Size and Accrual

Table 1: Sample size goals for HIV-infected infants

<table>
<thead>
<tr>
<th>Protocol Version</th>
<th>Regimen</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>2 NRTIs + NVP + LPV/r</td>
<td>34</td>
<td>20</td>
<td>54</td>
</tr>
<tr>
<td>2.0</td>
<td>2 NRTIs + NVP + RAL</td>
<td>Approximately 15</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs + NVP + RAL + VRC01</td>
<td>Approximately 15</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>All Version 2.0</td>
<td>30</td>
<td>15</td>
<td>45</td>
</tr>
</tbody>
</table>

This Phase I/II proof of concept exploratory study will follow breastfed and formula fed HIV-infected neonates who initiate early intensive therapy within 48 hours of birth. Infants will be enrolled either as high-risk neonates within 48 hours of birth (Cohort 1) or as in utero HIV-infected neonates who started a qualifying ART regimen (outside the study) within 48 hours of birth and are enrolled within 10 days of birth (Cohort 2).

Regimen 1L: 2 NRTIs + NVP + LPV/r
- Cohort 1: Approximately 440 to identify at least 22 with in utero HIV infection
- Cohort 2: Up to 32 with in utero HIV infection

Accrual of infants receiving Regimen 1L was completed under protocol Version 1.0; 34 in utero HIV-infected infants were enrolled in Cohort 1 and 20 in utero HIV-infected infants were enrolled in Cohort 2. At each site, once all required approvals of protocol Version 2.0 are obtained, follow-up of infants enrolled under protocol Version 1.0 will continue under protocol Version 2.0.

Regimen 2R: 2 NRTIs + NVP + RAL and Regimen 2RV (2 NRTIs + NVP + RAL + VRC01)
Regimen 2R and Regimen 2RV will be evaluated among infants enrolled under protocol Version 2.0. Approximately 430 mother-infant pairs will be enrolled in Cohort 1 to identify approximately 30 infants with in utero HIV infection receiving these two regimens, with the goal of having approximately equal distribution across the two regimens. An additional 15 mother-infant pairs enrolled in Cohort 2 will also receive Regimen 2R. Anticipated accrual of HIV-infected infants receiving each regimen is shown below; accrual of infants receiving each regimen may be adjusted if needed to enroll a total of 45 infants with in utero HIV infection receiving either Regimen 2R or Regimen 2RV.

Regimen 2R: 2 NRTIs + NVP + RAL
- Cohort 1: Approximately 215 to identify approximately 15 with in utero HIV infection receiving 2 NRTIs + NVP + RAL
- Cohort 2: 15 with in utero HIV infection receiving 2 NRTIs + NVP + RAL

Regimen 2RV: 2 NRTIs + NVP + RAL + VRC01
- Cohort 1: Approximately 215 to identify approximately 15 with in utero HIV infection receiving 2 NRTIs + NVP + LPV/r + VRC01
- Cohort 2 will not receive this regimen.
Under protocol Version 2.0, infants receiving Regimen 2R and infants receiving Regimen 2RV will be enrolled approximately concurrently. All study sites will be potentially eligible to enroll infants receiving Regimen 2R, but only selected sites will be eligible to enroll infants receiving Regimen 2RV, based on regulatory and pharmacy considerations for VRC01 as well as operational considerations for the study such as ensuring regimen target sample sizes. Sites’ regimen may be changed over time, but at no time will any site be enrolling infants receiving Regimen 2R and Regimen 2RV concurrently.

8.4.1 Sample Size for Cohort 1

In NICHD/HPTN 040, among HIV-infected mothers who did not receive antenatal ART (43), a total of 93 in utero HIV-infected infants were observed among 1684 non-breastfeeding infants; Kaplan-Meier estimate 5.7% (95% confidence interval 4.7-6.9).

Under P1115 protocol Version 1.0, 34 in utero HIV-infected infants were identified among 440 infants enrolled in Cohort 1 (7.7%). Under protocol Version 2.0, approximately 30 Cohort 1 infants with in utero HIV infection receiving Regimen 2R or Regimen 2RV are targeted to be enrolled. Assuming, based on experience under protocol Version 1.0, that 7% of infants enrolled in Cohort 1 are identified with in utero infection, 430 (30/0.07) infants will need to be enrolled in Cohort 1 to identify at least 30 HIV-infected infants in this cohort.

Table 2 summarizes the probabilities of observing 20-40 in utero HIV-infected neonates with a sample size of 430 assuming a true probability of observing an infected infant of 0.07 or 0.05 using a binomial distribution. If the transmission probability is 0.07, with a sample size of 430 infants enrolled in Cohort 1 under protocol Version 2.0, the probability of observing at least 30 in utero infected infants is 0.53. If the transmission probability is higher, for example, 0.08, with a sample size of 430, the probability of observing at least 30 in utero infected infants is 0.81.

Table 3 describes information that can be obtained over a range of sample sizes of between 10 and 40 in utero HIV-infected neonates who are followed for events of interest. Two types of events are of particular interest among very early treated in utero HIV-infected infants: HIV remission after ART cessation, and meeting criteria for ART cessation. For example, if the probability of HIV remission is 0.10 and 30 (15) very early treated in utero HIV-infected high-risk group (Cohort 1) children are enrolled then the probability of observing at least one HIV remission among those enrolled will be 0.96 (0.79). The probability of observing a remission decreases with decreasing sample size or decreasing probability of remission. The team feels that a remission probability less than 0.10 among very early treated in utero HIV-infected children would not warrant continued study of this concept. Similar statements can be made about the probability of meeting criteria for ART cessation. For example, assuming a hypothetical probability of 0.60 (0.40) for becoming eligible for ART cessation, with a sample size of 30 in utero HIV-infected children who are treated with ART, the probability of observing at least 15 children who are eligible for ART cessation is 0.9 (0.18).
Table 2: Probability of observing 20-40 in utero HIV-infected neonates with various sample sizes assuming a binomial distribution

<table>
<thead>
<tr>
<th>Sample size</th>
<th>True Probability of an event</th>
<th>At least number of events</th>
<th>Probability of observing the number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>430</td>
<td>0.05</td>
<td>20</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>0.00</td>
</tr>
<tr>
<td>0.06</td>
<td></td>
<td>20</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>0.00</td>
</tr>
<tr>
<td>0.07</td>
<td></td>
<td>20</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>0.04</td>
</tr>
<tr>
<td>0.08</td>
<td></td>
<td>20</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>0.18</td>
</tr>
</tbody>
</table>
Table 3: Probability of observing no event (e.g., HIV remission or meeting ART cessation criteria) and of observing at least 1-20 events with sample sizes of 10-40 (e.g., of Cohort 1 in utero HIV-infected children)

<table>
<thead>
<tr>
<th>N = Sample size</th>
<th>True Probability of an event</th>
<th>Probability of 0 event</th>
<th>≥ 1 event</th>
<th>≥ 5 events</th>
<th>≥ 10 events</th>
<th>≥ 15 events</th>
<th>≥ 20 events</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.01</td>
<td>0.90</td>
<td>0.10</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.05</td>
<td>0.60</td>
<td>0.40</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.1</td>
<td>0.35</td>
<td>0.65</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.2</td>
<td>0.11</td>
<td>0.89</td>
<td>0.03</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.3</td>
<td>0.03</td>
<td>0.97</td>
<td>0.15</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.4</td>
<td>0.01</td>
<td>0.99</td>
<td>0.37</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.5</td>
<td>0.00</td>
<td>1.00</td>
<td>0.62</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.6</td>
<td>0.00</td>
<td>1.00</td>
<td>0.83</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0.01</td>
<td>0.86</td>
<td>0.14</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0.05</td>
<td>0.46</td>
<td>0.54</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0.1</td>
<td>0.21</td>
<td>0.79</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0.2</td>
<td>0.04</td>
<td>0.96</td>
<td>0.16</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0.3</td>
<td>0.00</td>
<td>1.00</td>
<td>0.48</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0.4</td>
<td>0.00</td>
<td>1.00</td>
<td>0.78</td>
<td>0.03</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0.5</td>
<td>0.00</td>
<td>1.00</td>
<td>0.94</td>
<td>0.15</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0.6</td>
<td>0.00</td>
<td>1.00</td>
<td>0.99</td>
<td>0.40</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.01</td>
<td>0.82</td>
<td>0.18</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.05</td>
<td>0.36</td>
<td>0.64</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.1</td>
<td>0.12</td>
<td>0.88</td>
<td>0.04</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.2</td>
<td>0.01</td>
<td>0.99</td>
<td>0.37</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.3</td>
<td>0.00</td>
<td>1.00</td>
<td>0.76</td>
<td>0.05</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.4</td>
<td>0.00</td>
<td>1.00</td>
<td>0.95</td>
<td>0.24</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.5</td>
<td>0.00</td>
<td>1.00</td>
<td>0.99</td>
<td>0.59</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.6</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.87</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>0.01</td>
<td>0.78</td>
<td>0.22</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>0.05</td>
<td>0.28</td>
<td>0.72</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>0.1</td>
<td>0.07</td>
<td>0.93</td>
<td>0.10</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>0.2</td>
<td>0.00</td>
<td>1.00</td>
<td>0.58</td>
<td>0.02</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>0.3</td>
<td>0.00</td>
<td>1.00</td>
<td>0.91</td>
<td>0.19</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>0.4</td>
<td>0.00</td>
<td>1.00</td>
<td>0.99</td>
<td>0.58</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>0.5</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.89</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>0.6</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.99</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0.01</td>
<td>0.74</td>
<td>0.26</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0.05</td>
<td>0.21</td>
<td>0.79</td>
<td>0.02</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0.1</td>
<td>0.04</td>
<td>0.96</td>
<td>0.18</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0.2</td>
<td>0.00</td>
<td>1.00</td>
<td>0.74</td>
<td>0.06</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0.3</td>
<td>0.00</td>
<td>1.00</td>
<td>0.97</td>
<td>0.41</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0.4</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.82</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0.5</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.98</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0.6</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.01</td>
<td>0.67</td>
<td>0.33</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.05</td>
<td>0.13</td>
<td>0.87</td>
<td>0.05</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.1</td>
<td>0.01</td>
<td>0.99</td>
<td>0.37</td>
<td>0.01</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.2</td>
<td>0.00</td>
<td>1.00</td>
<td>0.92</td>
<td>0.27</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.3</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.80</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.4</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.98</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.5</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.6</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.93</td>
</tr>
</tbody>
</table>
Table 4 provides 95% confidence intervals on the event probability for various observed event numbers across a range of sample sizes of 10-40 (e.g., of very early treated *in utero* HIV-infected children).

For example, if HIV remission is observed in 1 out of 30 (15) very early treated high-risk *in utero* HIV-infected children, based on the 95% confidence interval, these data are consistent with a probability of remission between 0.00 and 0.17 (0.32). This confidence interval is also relevant if no remissions are observed. Notably, observing no remissions among 30 (15) very early treated high risk *in utero* HIV-infected children is consistent with a remission probability of 0 to 0.12 (0.22).

Another parameter of interest is the probability of meeting the criteria for ART cessation (eligibility for Step 3 entry) among the Cohort 1 *in utero* HIV-infected children. The probability is expected to be higher than the HIV remission among the very early treated (Cohort 1) *in utero* HIV-infected infants. If, for example, 10 out of 30 Cohort 1 *in utero* HIV-infected children meet the criteria for treatment cessation, the 95% confidence interval is 0.17 to 0.53. Notably again, for this event observing no one who meets criteria for ART cessation among 30 (15) Cohort 1 *in utero* HIV-infected children is consistent with a probability of meeting criteria of 0 to 0.12 (0 to 0.22).

Also of interest is the probability of remission among the children who cease ART. Table 4 provides that, based on the 95% confidence interval, observing 0 out of 10 remissions among the children who cease ART is consistent with a probability of remission ranging from 0 to 0.31.
Table 4: 95% confidence interval (CI) for the probability of an event (e.g., HIV remission) with sample sizes (and event numbers) of 10-40 (e.g., of Cohort 1 in utero HIV-infected children)

<table>
<thead>
<tr>
<th>N = Sample size</th>
<th>N of events</th>
<th>Proportion with an event</th>
<th>95% CI Lower bound</th>
<th>95% CI Upper bound</th>
<th>Width</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.31</td>
<td>0.31</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>0.10</td>
<td>0.00</td>
<td>0.45</td>
<td>0.44</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>0.50</td>
<td>0.19</td>
<td>0.81</td>
<td>0.63</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>1.00</td>
<td>0.69</td>
<td>1.00</td>
<td>0.31</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.22</td>
<td>0.22</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>0.07</td>
<td>0.00</td>
<td>0.32</td>
<td>0.32</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
<td>0.33</td>
<td>0.12</td>
<td>0.62</td>
<td>0.50</td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>0.67</td>
<td>0.38</td>
<td>0.88</td>
<td>0.50</td>
</tr>
<tr>
<td>15</td>
<td>15</td>
<td>1.00</td>
<td>0.78</td>
<td>1.00</td>
<td>0.22</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>20</td>
<td>1</td>
<td>0.05</td>
<td>0.00</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
<td>0.25</td>
<td>0.09</td>
<td>0.49</td>
<td>0.40</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>0.50</td>
<td>0.27</td>
<td>0.73</td>
<td>0.46</td>
</tr>
<tr>
<td>20</td>
<td>15</td>
<td>0.75</td>
<td>0.51</td>
<td>0.91</td>
<td>0.40</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td>1.00</td>
<td>0.83</td>
<td>1.00</td>
<td>0.17</td>
</tr>
<tr>
<td>25</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.14</td>
<td>0.14</td>
</tr>
<tr>
<td>25</td>
<td>1</td>
<td>0.04</td>
<td>0.00</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>25</td>
<td>5</td>
<td>0.20</td>
<td>0.07</td>
<td>0.41</td>
<td>0.34</td>
</tr>
<tr>
<td>25</td>
<td>10</td>
<td>0.40</td>
<td>0.21</td>
<td>0.61</td>
<td>0.40</td>
</tr>
<tr>
<td>25</td>
<td>15</td>
<td>0.60</td>
<td>0.39</td>
<td>0.79</td>
<td>0.40</td>
</tr>
<tr>
<td>25</td>
<td>20</td>
<td>0.80</td>
<td>0.59</td>
<td>0.93</td>
<td>0.34</td>
</tr>
<tr>
<td>25</td>
<td>25</td>
<td>1.00</td>
<td>0.86</td>
<td>1.00</td>
<td>0.14</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>30</td>
<td>1</td>
<td>0.03</td>
<td>0.00</td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
<td>0.17</td>
<td>0.06</td>
<td>0.35</td>
<td>0.29</td>
</tr>
<tr>
<td>30</td>
<td>10</td>
<td>0.33</td>
<td>0.17</td>
<td>0.53</td>
<td>0.36</td>
</tr>
<tr>
<td>30</td>
<td>15</td>
<td>0.50</td>
<td>0.31</td>
<td>0.69</td>
<td>0.37</td>
</tr>
<tr>
<td>30</td>
<td>20</td>
<td>0.67</td>
<td>0.47</td>
<td>0.83</td>
<td>0.36</td>
</tr>
<tr>
<td>30</td>
<td>25</td>
<td>0.83</td>
<td>0.65</td>
<td>0.94</td>
<td>0.29</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
<td>1.00</td>
<td>0.88</td>
<td>1.00</td>
<td>0.12</td>
</tr>
<tr>
<td>35</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>35</td>
<td>1</td>
<td>0.03</td>
<td>0.00</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>35</td>
<td>5</td>
<td>0.14</td>
<td>0.05</td>
<td>0.30</td>
<td>0.25</td>
</tr>
<tr>
<td>35</td>
<td>10</td>
<td>0.29</td>
<td>0.15</td>
<td>0.46</td>
<td>0.32</td>
</tr>
<tr>
<td>35</td>
<td>15</td>
<td>0.43</td>
<td>0.26</td>
<td>0.61</td>
<td>0.34</td>
</tr>
<tr>
<td>35</td>
<td>20</td>
<td>0.57</td>
<td>0.39</td>
<td>0.74</td>
<td>0.34</td>
</tr>
<tr>
<td>35</td>
<td>25</td>
<td>0.71</td>
<td>0.54</td>
<td>0.85</td>
<td>0.32</td>
</tr>
<tr>
<td>35</td>
<td>30</td>
<td>0.86</td>
<td>0.70</td>
<td>0.95</td>
<td>0.25</td>
</tr>
<tr>
<td>35</td>
<td>35</td>
<td>1.00</td>
<td>0.90</td>
<td>1.00</td>
<td>0.10</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>40</td>
<td>1</td>
<td>0.03</td>
<td>0.00</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>40</td>
<td>5</td>
<td>0.13</td>
<td>0.04</td>
<td>0.27</td>
<td>0.23</td>
</tr>
<tr>
<td>40</td>
<td>10</td>
<td>0.25</td>
<td>0.13</td>
<td>0.41</td>
<td>0.29</td>
</tr>
<tr>
<td>40</td>
<td>15</td>
<td>0.38</td>
<td>0.23</td>
<td>0.54</td>
<td>0.31</td>
</tr>
<tr>
<td>40</td>
<td>20</td>
<td>0.50</td>
<td>0.34</td>
<td>0.66</td>
<td>0.32</td>
</tr>
<tr>
<td>40</td>
<td>25</td>
<td>0.63</td>
<td>0.46</td>
<td>0.77</td>
<td>0.31</td>
</tr>
<tr>
<td>40</td>
<td>30</td>
<td>0.75</td>
<td>0.59</td>
<td>0.87</td>
<td>0.29</td>
</tr>
<tr>
<td>40</td>
<td>35</td>
<td>0.88</td>
<td>0.73</td>
<td>0.96</td>
<td>0.23</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
<td>1.00</td>
<td>0.91</td>
<td>1.00</td>
<td>0.09</td>
</tr>
</tbody>
</table>
8.4.2 Sample Size for Cohort 2

Up to 32 infants receiving Regimen 1L will be enrolled in Cohort 2 under Version 1.0 and up to 15 infants receiving Regimen 2R will be enrolled in Cohort 2 under Version 2.0. The tables above provide information on the precision for estimating event probabilities within the range of these sample sizes.

8.4.3 Accrual

Accrual to the high-risk infants in Cohort 1 will depend on identifying high-risk infants. Assuming the Version 1.0 accrual rate will continue at a similar number of sites the team anticipates enrolling 150 to 200 infants per year once sites are activated for Version 2.0. The target sample size for Version 2.0 is estimated to be reached within 3 years (counted from the date of first enrollment under protocol Version 2.0).

8.5 Monitoring

A full study monitoring plan with more specific details was prepared before the study opened to accrual under Protocol Version 1.0 and will be updated as needed for protocol Version 2.0.

8.5.1 Anticipated Accrual

Accrual into this study will be monitored by the IMPAACT leadership in accordance with standard operating procedures. The team will assess for barriers to accrual, if any, on a quarterly basis, after the majority of the sites have received approval for the updated protocol version. Initially, the team will monitor activation of sites to initiate the protocol quarterly to ensure that the number of sites participating is sufficient to complete the study. If less than one-half of eligible IMPAACT sites have been activated within 12 months after the protocol is opened to accrual under Version 2.0, the team will re-assess the feasibility of the protocol, examine the reasons why sites have not been activated, and will possibly amend the protocol accordingly. Once one-half of eligible IMPAACT sites have been activated under Version 2.0, the team will assess for barriers to accrual, if any, on a quarterly basis. If fewer than 100 infants have been enrolled within 12 months after one-half of all eligible IMPAACT sites have opened to enrollment, the team will identify and address the reasons for lack of accrual.

8.5.2 Routine Monitoring

The CMC will have regular conference calls to ensure that its members are aware of ongoing issues concerning the conduct of the study. The CMC will monitor safety closely. Safety and toxicity reports summarizing laboratory and clinical data from the study database (CRFs and laboratory data) will be reviewed regularly by the CMC.

In addition to regular toxicity reviews by the CMC, the study will be monitored every 12 months or on a schedule as specified by an independent Study Monitoring Committee (SMC) according to standard IMPAACT procedures. Potential safety issues that arise from CMC reviews will be brought to the attention of the SMC.
8.5.3 Interim Monitoring by SMC

At scheduled reviews, the SMC will review study conduct, including accrual, retention and safety. This review will take place at least every 12 months or on a schedule specified by the SMC. The primary safety outcome data will be reviewed, as well as permanent discontinuations of ARVs for safety reasons.

Additionally, the SMC will review the proportion of Cohort 1 infants who are identified as in utero HIV-infected and the proportions of in utero HIV-infected children who meet criteria for ART cessation in order to assess sample size calculation assumptions and to provide input on any proposed adjustments to sample sizes.

Scenarios in which a sample size adjustment might be considered include:

Increase the number of infants to be enrolled; this might occur if the proportion of Cohort 1 infants who are in utero infected or the proportion of infants meeting ART cessation criteria is lower than assumed.

In addition to the regularly scheduled SMC reviews, an ad hoc SMC review may be triggered for safety, ART cessation or ART re-initiation related reasons.

8.5.3.1 Guideline for Accrual Monitoring

If by three years after the study opens to accrual under Version 2.0, fewer than 20 HIV-infected infants have been enrolled into Cohort 1 under Version 2.0 (e.g., due to challenges with identifying and enrolling high risk mother-infant pairs or due to a lower than anticipated HIV transmission rate), the SMC will assess the futility of reaching the targeted sample size for this cohort or the team might seek guidance from IMPAACT and DAIDS leadership on whether accrual in that cohort or in the entire study should continue.

8.5.3.2 Guidelines for Triggering a Safety Review

Triggers for safety reviews will require assessing drug relatedness for an event. Relatedness will be based on reports from the site and adjudication by the CMC. Ad hoc review safety triggers will be based on data that are combined across both cohorts.

For All Infants
All infants (to the time when the HIV infection is confirmed, which includes HIV uninfected and infected infants): the proportion of infants who permanently discontinue any ARV due to a possibly, probably or definitely related toxicity or have a safety outcome as defined in Section 8.2.2.1 Grade 3 or higher adverse events possibly, probably or definitely related to any component of the study regimen. These outcomes will be based on data collected through CRFs. Relatedness will be based on reports from the site with adjudication by the CMC. will be monitored. An SMC review for safety will be triggered if, after 30 infants have been enrolled:

- This proportion is \( \geq 0.10 \) for non-hematologic events.
- This proportion is \( \geq 0.20 \) for hematologic events.

Similarly, among all infants, mortality will be monitored. An SMC review will be triggered if any death occurs that is possibly, probably or definitely related to any ARV.
Enrollment into the study will be suspended if any of the above-listed triggers for all infants are met, pending the outcome of the SMC review.

**For HIV-Infected Infants**

HIV-infected infants: An SMC review for safety will be triggered if two of any of the following occur among infants receiving a given regimen (i.e., Regimen 1L, 2R, or 2RV):

a) life-threatening event assessed as possibly, probably or definitely related to an ARV other than an NRTI OR
b) life-threatening event assessed as possibly, probably or definitely related to VRC01 OR
c) permanent discontinuation of an ARV other than an NRTI for toxicity assessed as possibly, probably, or definitely related to that ARV OR
d) permanent discontinuation of VRC01 for toxicity assessed as possibly, probably, or definitely related to VRC01

If the above-listed triggers for HIV-infected infants are met based on the occurrence of two non-hematologic events (among infants receiving a given regimen), enrollment into the study will be paused pending the outcome of the SMC review. Otherwise, the CMC will determine whether to suspend or continue accrual pending the outcome of the SMC review.

*Note: Under protocol Version 1.0, the SMC chose to review hematological triggering events for HIV-infected infants on a routine periodic basis rather than ad hoc as events occurred. The same approach may be taken under protocol Version 2.0, if requested by the SMC.*

After a safety trigger for HIV-infected infants has been met, and the required SMC review has taken place, the threshold for future triggers will be reset (i.e., the two events that triggered a safety review will not be re-counted as triggers toward future reviews).

An SMC review will also be triggered based on the proportion of HIV-infected infants experiencing the above-listed events. A review will be triggered if, after 30 HIV-infected have been enrolled:

- This proportion is ≥ 0.20 for non-hematologic events.
- This proportion is ≥ 0.30 for hematologic events.

### 8.5.3.3 Guideline for Triggering a Review of ART Cessation due to Viral Rebound

Guidelines for a review will be applied separately by Version of enrollment (regimen 1L separately from 2R + 2RV combined). If 10 out of the first 10 children in Step 3 who cease taking ART have viral rebound within 48 weeks, ART cessation will be suspended for an *ad hoc* SMC review to evaluate the future direction for this protocol (enrollment into the study will not be suspended). ART cessation suspension guidelines are not specified if fewer than 10 children have ceased taking ART.

Given the small sample sizes the information available for decisions based on this guideline will be imperfect. The team does not feel that viral rebound is a safety issue, and the concern here is whether the probability of remission is low. An error for applying this pausing guideline would occur if the guideline is met when the true HIV-remission probability is still acceptable (not too low). *Table 5* shows the probability that the guideline for pausing ART cessation will be met under a range of hypothetical true rebound probabilities.
Table 5: Probability of meeting the guidelines to pause ART cessation for an ad hoc SMC review under a range of hypothetical true rebound probabilities

Guideline = first 10 of 10 children have viral rebound within 48 weeks of ART cessation (i.e., 0 of 10 achieve with HIV remission as defined for this study)

<table>
<thead>
<tr>
<th>True probability of rebound (P)</th>
<th>True probability of remission (1-P)</th>
<th>Probability of Meeting Pausing Guideline for SMC review</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30</td>
<td>0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.50</td>
<td>0.50</td>
<td>0.001</td>
</tr>
<tr>
<td>0.70</td>
<td>0.30</td>
<td>0.03</td>
</tr>
<tr>
<td>0.80</td>
<td>0.20</td>
<td>0.11</td>
</tr>
<tr>
<td>0.90</td>
<td>0.10</td>
<td>0.35</td>
</tr>
<tr>
<td>0.95</td>
<td>0.05</td>
<td>0.60</td>
</tr>
<tr>
<td>0.99</td>
<td>0.01</td>
<td>0.90</td>
</tr>
</tbody>
</table>

For example, the probability of meeting the guideline for pausing ART cessation is 0.11 if the true probability of viral load rebound is 0.80 (probability of remission as high as 0.20). If the true probability of viral load rebound is high, for example 0.99, the probability of meeting the guideline for pausing ART cessation is 0.90.

8.5.3.4 Guideline for Triggering a Review of ART Cessation due to lack of Re-suppression among Children who Experience Viral Rebound after ART Cessation

Guidelines for triggering a review will be applied separately to each cohort. If 5 children do not re-suppress (confirmed < 200 copies/mL) by 12 weeks after ART re-initiation, ART cessation will be suspended in that cohort for an ad hoc SMC review to evaluate the future direction for this protocol (enrollment into the study will not be suspended).

8.5.3.5 Considerations if HIV Remission is Observed

If remission is observed, enrollment to the projected sample size and follow up will continue in order to quantify the probability of remission, to study the generalizability of the result and to identify key parameters that need to be monitored to achieve remission. The team will have ongoing discussion and seek input from the SMC regarding public dissemination of information on remission(s) in this protocol. Other ancillary data such as PK results may be published as needed prior to completion of follow up.

8.6 Analyses

Analyses will be carried out separately for in utero HIV-infected infants from each cohort (Cohort 1 and Cohort 2), as well as by LPV/r-containing and RAL-containing (combined 2R and 2RV) regimen. Primary analysis will be based on Cohort 1. Secondary analyses will be carried out within feeding method and by regimen (LPV/r- and each RAL-containing regimen).

This is a Phase I/II proof of concept exploratory study. The primary analysis will consist of descriptive statistics. Data summaries will provide point estimates with corresponding 95% confidence intervals for parameters of interest. For example, the proportion of in utero HIV-infected neonates from Cohort 1 who meet the definition for HIV remission will be provided, along with a 95% confidence interval on this probability. For this outcome, children who discontinue study follow-up prior to study completion will be treated as not achieving remission.
Supplemental analyses will evaluate the sensitivity of results to different approaches to handling missing data.

Summary tables, figures or listings will be provided for major secondary outcome measures of eligibility for ART cessation, HIV virology related outcomes, including duration of remission (time to rebound), and for the safety outcome. Point estimates for parameters of interest will be presented, along with 95% confidence intervals.

Safety data will be summarized for 3 groups under each regimen (LPV/r- and each RAL-containing regimen): a) all infants through the time when HIV infection is confirmed; b) HIV-uninfected infants; c) \textit{in utero} HIV-infected infants.

A detailed statistical analysis plans describing analyses of both maternal and infant study data will be developed separately.

9.0 \textbf{CLINICAL PHARMACOLOGY PLAN}

9.1 Pharmacology Objectives

- To describe RAL and VRC01 exposures in neonates and young infants.

A preliminary NVP dose evaluation was completed under protocol Version 1.0; based on this evaluation, 6 mg/kg dose was determined to be the optimal dose for full term neonates and infants in this study. Further population PK analyses of NVP, LPV, and RTV will be performed using dried blood spot (DBS) samples collected under protocol Version 1.0, as described in protocol Version 1.0.

The remainder of this section describes analyses planned to describe RAL and VRC01 exposures based on samples collected from infants receiving Regimen 2R and Regimen 2RV under protocol Version 2.0.

9.2 Primary and Secondary Data

9.2.1 RAL

Whole blood samples will be collected for RAL quantitation in plasma at Step 1 Week 1, Step 1 Week 2 (if still on RAL), Step 2 Entry, Step 2 Week 1, Step 2 Week 2, and Step 2 Week 4. In Step 1, the expected combined sample size for Regimens 2R and 2RV is 430; in Step 2, the expected combined sample size is 45.

9.2.2 VRC01

Whole blood samples will be collected for VRC01 quantitation in plasma at Step 1 Week 1, Step 2 Entry, and Step 2 Weeks 4, 8, 12, 16, 20 and 24. At Step 2 Entry, Week 4, and Week 8, samples will be collected prior to administration of VRC01. In Step 1, the expected sample size for Regimen 2RV is 215; in Step 2, the expected sample size is 15.
9.3 Laboratory Analysis and Reporting

Plasma samples for RAL and VRC01 concentration determination will be collected, stored, and later shipped to designated laboratories for batched testing. All samples will be registered in the Laboratory Data Management System. Data collected on PK CRFs will be provided to the pharmacologists for analysis by the Data Management Center. These data will include gestational age at birth, postnatal age, gender, current weight, current height, dose, date and time of the current and most recent doses, date and times of sample collections and all relevant comments on the PK CRFs.

9.4 Study Design, Modeling, and Data Analysis

9.4.1 RAL

Samples for RAL quantitation will be collected as described above. At each time point, whole blood will be collected, processed to plasma, and frozen for batched testing. Previous dose amount, dose date/time, and sample draw date/time will be recorded, as well as other covariates. As prior RAL modeling work has been done for IMPAACT P1110, simulations from the P1110 model will be compared with RAL concentrations in P1115. Data from P1115 will be compared directly to simulated 10th, 25th, 50th, 75th, and 90th percentile concentration-time curves, using the same dosing regimen, to determine how well the P1115 data compare to previously collected robust datasets. This approach will not yield individual PK parameters for RAL in P1115 but will indicate how well the concentration data compare (e.g., higher or lower or similar) to prior data.

9.4.2 VRC01

Samples for VRC01 quantitation will be collected as described above. At each time point, whole blood will be collected, processed to plasma, and frozen for batched testing. Previous dose amount, dose date/time, and sample draw date/time will be recorded, as well as other covariates. The VRC01 PK data expected from this study are too sparse for a full standard non-compartmental analysis. The elimination rate constant, λz, and associated half-life will be estimated from the terminal portion of log VRC01 concentration versus time profile. Since the total number of P1115 participants contributing VRC01 concentration data are too few for an independent population analysis, the observed P1115 concentrations will be compared to those predicted from the IMPAACT P1112 PK model. Simulations will be generated based on the dosing in P1115 and the P1112 PK parameters. The observed VRC01 concentrations in P1115 will be directly compared to simulated 10th, 25th, 50th, 75th, and 90th percentile concentration-time curves from the P1112 PK model.

In addition, a nested population PK analysis that combines raw VRC01 PK data from P1115 and P1112 will be performed. A two-compartment PK model will be employed using the computer program NONMEM. The population analysis will generate estimates for initial and final apparent volumes of distribution (V1/F and V2/F), inter-compartmental clearance (Q/F), CL/F and the absorption rate constant, KA. Weight will be assumed to be a relevant covariate and included in the model. Given the small number of participants, the population PK analysis will include only a limited exploratory covariate analysis to assess clinical factors as fixed effects associated with VRC01 PK. Specifically, dose (20 mg/kg versus 40 mg/kg), study (P1112 versus P1115) and postnatal age will be assessed as potential fixed effects on F, CL and V1/V2.
Final population PK model selection will be based on changes in the objective function and graphically by goodness of fit plots. The final population model parameters will be assessed using bootstrapping to generate 95% CIs for parameter estimates and by visual posterior predictive check. Post-hoc empiric Bayesian estimates of individual P1115 participant’s PK parameters may be generated. Monte Carlo simulations using the population parameters and their variability will be used to characterize the distribution of VRC01 concentrations from the P1115 VRC01 dosing regimen.

10.0 **HUMAN SUBJECTS**

10.1 Institutional Review Board/Ethics Committee and Informed Consent

This protocol, ICFs (see APPENDIX IV), and any subsequent modifications must be reviewed and approved by the IRBs/ECs and other applicable REs responsible for oversight of the study. In order for infants to take part in this study, their mothers must be available, willing, and able to provide written informed consent for both maternal and infant participation in the study. For infants eligible for Step 1 (Cohort 1), informed consent will first be obtained for participation in that step. Separately, for infants eligible to take part in Step 2 (Cohort 1 or Cohort 2), informed consent will be obtained for that step. For infants eligible for Step 3, separate informed consent will be obtained for that Step 3 and Step 4 (see Section Evaluation to Determine Eligibility for Treatment Cessation for a description of information to be discussed with mothers/parents/guardians of children found to be eligible for Step 3, prior to cessation of ART). Copies of the ICFs will be offered to the consenting mother/parent/guardian.

Each site that receives US Department of Health and Human Service (DHHS) funding and follows the US Code of Federal Regulations Title 45-Public Welfare, Part 46-Protection of Human Subjects (also known as the Common Rule) should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric participants and determines when a participant must have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. The plan will include how the site determines when a LAR is initially or no longer needed and how frequently the LAR re-signs the consent. The plan should follow all IRB/EC, local, state, national and/or host country guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

10.2 Essential and Source Documents and Access to Source Data

Study sites must comply with DAIDS policies on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. In its policy on Requirements for Manual of Operational Procedures, DAIDS requires sites to establish SOPs for maintaining essential and source documents in compliance with these policies. Site SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study, and site SOPs should be followed throughout the study.
Per the DAIDS policy on Storage and Retention of Clinical Research Records, study records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility during the conduct of the study and after the study is completed. Records must be retained for a minimum of three years after the completion of the study. Per 21 CFR 312.62, records must be maintained for two years after the date a marketing application is approved for one or more of the study products for the indication for which it is evaluated in this study; or, if no application is filed, or if the application is not approved for this indication, records must be retained two years after the study is discontinued and the FDA is notified.

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, IMPAACT, Merck Research Laboratories, the Vaccine Research Center, the FDA, the US Office for Human Research Protections, site drug regulatory authorities, site IRBs/ECs, and other US, local, and international regulatory entities. Records must be kept on-site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID or NICHD. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID or NICHD.

10.3 Participant Confidentiality

Study procedures will be conducted in private and every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing. If any photographs of observed reactions are taken, standard precautions will be followed to ensure that participant privacy and confidentiality are protected.

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site (e.g., EAE report forms, photographs of observed reactions) will be identified by PID only. Likewise, communications between study staff and protocol team members regarding individual participants will identify participants by PID only.

Study sites are encouraged but not required by DAIDS policies to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

In addition to the above, a Certificate of Confidentiality has been obtained for this study from the US DHHS. This certificate protects study staff from being compelled to disclose study-related information by any US federal, state, or local civil, criminal, administrative, legislative, or other proceedings. It thus serves to protect the identity and privacy of study participants. Because the certificate cannot be enforced outside of the US, however, it applies only to US sites and participants.

10.4 Study Discontinuation

The study may be discontinued at any time by the sponsors, IMPAACT, government or regulatory authorities, or site IRBs/ECs.
10.5 Post-Study Access to Study Agents

Two agents of the study regimens, VRC01 and RAL, will be provided through this study.

This study will provide information on the safety and antiviral activity of VRC01 as part of an early intensive ART regimen. Based on the results of this study, other studies may be conducted in the future to further characterize the safety and efficacy of VRC01 for this population. Before such studies are completed, the efficacy of VRC01 and its risk-to-benefit ratio for this population remain unknown; therefore, VRC01 may not be immediately available after this study is completed. Should future studies demonstrate clinical benefit from use of VRC01, the VRC intends to develop the product (or other related products) so that it can be made available for appropriate indications.

The chewable/dispersible tablet formulation of RAL is currently registered in Argentina, Brazil, Kenya, South Africa, Malawi, the US, Tanzania, Thailand, and Zimbabwe. In Haiti and Uganda, the chewable tablet formulation is not currently registered but can be obtained by requesting an import license from the Ministry of Health. Although pediatric formulations of RAL are not yet widely available in public sector HIV treatment programs worldwide, availability is expected to increase as this study is being conducted. As such, it is expected that HIV-infected infants who may be benefiting from use of RAL during the study may be able to access RAL from local HIV care and treatment programs when their study participation ends. If RAL is not locally available through such programs, Merck Research Laboratories and/or their partners will make every effort to provide RAL to (former) study participants through non-study mechanisms, until RAL becomes available locally. Despite the company’s efforts, however, post-study access to RAL cannot be guaranteed. For any infants who are not able to access RAL from local HIV care and treatment programs or through other non-study mechanisms, adverse consequences are not expected upon switching to an alternate regimen when their study participation ends.

11.0 PUBLICATION OF RESEARCH FINDINGS

All presentations and publication of data collected in this study are governed by IMPAACT policies, which are available in the IMPAACT Manual of Procedures.

12.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as currently recommended by the US Centers for Disease Control and Prevention, NIH, and other applicable agencies. All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association (IATA) Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650; for UN 2814, Biological Substances, Category A, and Packing Instruction 620 if culture isolates are obtained for this study; and the Class 9 miscellaneous label, UN 1845 with the net weight (kg) of dry ice according to Packing Instruction 904.
13.0 REFERENCES


APPENDIX I
MATERNAL SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th>Mothers of all infants (HIV-uninfected and HIV-infected)¹</th>
<th>Mothers of HIV-infected infants only²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entry</strong> When infant is confirmed infected (at time of infant Step 2 entry)</td>
<td><strong>Every 6 months (± 6 weeks)</strong></td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLINICAL EVALUATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>History³,⁴</td>
</tr>
<tr>
<td>X</td>
</tr>
<tr>
<td>Every 6 months while infant is on study</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LABORATORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmatory HIV testing if needed³</td>
</tr>
<tr>
<td>HIV RNA⁵</td>
</tr>
<tr>
<td>CD4</td>
</tr>
<tr>
<td>Stored serum⁶</td>
</tr>
<tr>
<td>Stored plasma and cells⁵</td>
</tr>
<tr>
<td>10 mL or 20 mL</td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME</td>
</tr>
<tr>
<td>15 or 25 mL</td>
</tr>
</tbody>
</table>

For mothers enrolled in Cohort 1, evaluations listed under “Entry” should be performed on the day of entry into Cohort 1, and evaluations listed under “When infant is confirmed infected” should be performed on the day of entry into Step 2. For mothers enrolled in Cohort 2, evaluations listed under “Entry” and under “When infant is confirmed infected” should be performed on the day of entry into Step 2.

1. Mothers of infants in whom in utero HIV infection is excluded will be taken off study after the mother’s Entry visit and the infant’s Step 1 Week 12 visit have been completed.
2. Mothers of infants in whom in utero HIV infection is confirmed will be followed every 6 months for as long as the infant remains on study.
3. Targeted history including documentation of HIV infection, WHO clinical staging, maternal ARV use (all ARVs taken prior to study entry), CD4 T cell and HIV RNA results within the last year (based on available medical record documentation), obstetrical history including prior pregnancies and mode of delivery for the current pregnancy; syphilis in the current pregnancy (based on available medical record documentation), and active hepatitis at the time of study entry (based on available medical record documentation). If documentation of HIV infection meeting requirements in Section 4.1.1.1 is not available, blood should be collected for additional testing meeting protocol requirements. At least one positive HIV rapid test result must be available prior to entry and confirmatory results meeting protocol requirements must be available within 10 business days after study entry; otherwise, the mother and infant must be discontinued from the study.
4. Targeted interval history including WHO clinical staging, maternal ARV use, and chart abstraction for CD4 T cells and HIV RNA if available.
5. HIV RNA must be performed at a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory at the time of study entry.
6. Blood will be stored (serum, plasma, cells) for: HIV RNA, HIV drug and VRC01 resistance, HIV subtype, sequencing and immune studies which may include HLA typing, CCR5 delta 32 genotyping, and single nucleotide polymorphism for related host genetic factors. For mothers enrolled in Cohort 1, 10 mL should be collected for stored plasma and cells on the day of entry into Step 1 and an additional 10 mL should be collected on the day of entry into Step 2 (if entry into Step 2 occurs). For mothers enrolled in Cohort 2, 20 mL should be collected for stored plasma and cells on the day of entry into Step 2.

Unless otherwise specified, stored samples are retained locally until requested by the team for shipment to the repository or the designated centralized testing laboratory for batched testing.
## APPENDIX II-A
### INFANT SCHEDULE OF EVALUATIONS
#### STEP 1

<table>
<thead>
<tr>
<th></th>
<th>Step 1 Entry (≤48 hours of birth)</th>
<th>Week 1 (± 2 days)</th>
<th>Week 2* (± 2 days)</th>
<th>Week 4* (± 1 wk)</th>
<th>Week 12* (± 2 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History¹</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical exam²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>VRC01 administration³</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactogenicity⁵</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology⁴</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0-0.5 mL⁶</td>
<td></td>
</tr>
<tr>
<td>Chemistries⁵</td>
<td>1.0 mL</td>
<td>1.0 mL</td>
<td>1.0 mL</td>
<td>0-1.0 mL⁶</td>
<td></td>
</tr>
<tr>
<td><strong>VIROLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV nucleic acid⁷</td>
<td>Sample 1: 1.5-3.0mL</td>
<td>1.5-3.0 mL</td>
<td>1.5-3.0 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored plasma and PBMCs⁸</td>
<td>3.0 mL</td>
<td>2.0 mL</td>
<td></td>
<td>1.0 mL</td>
<td></td>
</tr>
<tr>
<td><strong>STUDY AGENT CONCENTRATIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAL⁹</td>
<td>X</td>
<td></td>
<td>0.15 mL¹⁰</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VRC01⁹</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME</td>
<td>7.5-10.5 mL</td>
<td>3.5 mL</td>
<td>3.15-4.65 mL</td>
<td>0-1.5 mL</td>
<td>2.5-4 mL</td>
</tr>
</tbody>
</table>

Day of study entry = Day 0 for this schedule. The Step 1 Entry visit may be conducted as a split visit; see Section 6.3.1 for more information.

*Infants with confirmed in utero HIV infection (see Section Evaluation and Initial Treatment of High-Risk Infants (Step 1)) will remain on the study regimen and enter Step 2 (APPENDIX II-B) instead of completing the Step 1 Week 2, Week 4, and Week 12 visits. Infants without confirmed in utero HIV infection will complete the Step 1 visits shown above and exit the study after completing the Week 12 visit. These infants will discontinue the study regimen and switch to standard perinatal prophylaxis per local guidelines as soon as possible after infection is excluded (no later than the Week 2 visit).
APPENDIX II-A
STEP 1 FOOTNOTES

1. **At Entry**, history should include sex and race/ethnicity; weight, length, head circumference, and gestational age at birth (based on available medical record documentation); clinical history (diagnoses, signs, symptoms); ARVs and other concomitant medications; interventions for hyperbilirubinemia; method of feeding; and all HIV tests since birth. **After Entry**, interval history should include clinical history (diagnoses, signs, symptoms); ARVs and other concomitant medications; interventions for hyperbilirubinemia; and method of feeding. All history should be recorded in source documents. The following should be recorded on CRFs: feeding history, all Grade ≥ 2 signs and symptoms, all signs and symptoms (regardless of grade) that lead to a change of study regimen (including any change of any ARV), all diagnoses except those noted on the “do not record” list (available at www.fstrf.org), all HIV tests, all ARVs, all concomitant medications, and all interventions for hyperbilirubinemia. At Week 12, only record HIV testing history since Week 4.

2. Physical exam includes temperature, heart rate, respiratory rate, weight, length, head circumference, breath sounds, heart sounds; additionally **at Entry**, examination of skin, head, mouth, neck, abdomen, extremities; additionally **after Entry**: examination of body systems driven by prior and new signs, symptoms, and diagnoses. For infants receiving Regimen 2RV, examination of extremities includes the VRC01 injection site.

3. Infants receiving Regimen 2RV will be administered VRC01 at the Entry visit and will be monitored for reactogenicity by site clinicians per Section 6.2.5. Infant caregivers will also be instructed to complete a memory aid document to record infant signs and symptoms for seven days (beginning on the day of administration).

4. Hematology: Complete blood count with differential and platelet count. At Entry, tests performed in the standard of care setting prior to study entry may be used for study purposes (i.e., if adequately documented results are available, the tests need not be repeated).

5. Chemistries: AST, ALT, ALP, total bilirubin, creatinine. At Entry, tests performed in the standard of care setting prior to study entry may be used for study purposes (i.e., if adequately documented results are available, the tests need not be repeated).

6. Perform at Week 4 only if Week 2 result is Grade ≥ 1.

7. HIV DNA PCR, quantitative and qualitative HIV RNA PCR, and HIV TNA PCR are acceptable. At Entry, two separate blood draws at least one hour apart are required. Both draws should ideally occur within 48 hours of birth. If this is not possible, the second sample may be collected within 12 hours after the first sample; the first sample must be collected within 48 hours of birth. One test must be a quantitative HIV RNA PCR; the second test can also be a quantitative HIV RNA PCR, but an HIV DNA PCR or an HIV TNA PCR is desirable. At least one test must be performed at a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory. Results must be available by Week 2. Any residual samples (whole blood, plasma, cell pellets, other) should be stored for additional testing if needed.

8. Samples will be used for additional HIV nucleic acid testing if needed to clarify HIV status and to identify host and viral factors associated with HIV remission, including HIV drug and VRC01 resistance testing and viral sequencing. Samples for host and viral factors will be tested at the designated central pathogenesis laboratory (samples from uninfected infants will be used as controls for these evaluations). Samples from infected infants may be used for droplet digital DNA PCR.

9. At Week 1, plasma aliquots for RAL and VRC01 concentrations will be obtained from the 2.5 mL of blood collected for plasma and PBMC storage.

10. At Week 2, collect sample for RAL concentration only if RAL was continued between Week 1 and Week 2.

Unless otherwise specified, all stored samples are retained locally until requested by the team for shipment to the repository or the designated centralized testing laboratory for batched testing.

NIH recommended pediatric blood collection limits of 5 mL/kg in a single day and 9.5 mL/kg in any 8-week period should be followed. Refer to the blood draw priority list below. All sites should comply with IRB/EC limitations.

**Blood draw priority list**

1. Virology
2. Hematology
3. Chemistries
4. Study agent concentrations
## APPENDIX II-B

### INFANT SCHEDULE OF EVALUATIONS

**STEP 2: ENTRY THROUGH WEEK 9**

<table>
<thead>
<tr>
<th></th>
<th>Step 2 Entry¹</th>
<th>Entry +3d (±1/+3d)</th>
<th>Week 1 (± 2 days)</th>
<th>Week 2 (± 2 days)</th>
<th>Week 4 (± 1 wk)</th>
<th>Week 4 +3d (±1/+3d)</th>
<th>Week 5 (± 2 days)</th>
<th>Week 8 (± 1 wk)</th>
<th>Week 8 +3d (±1/+3d)</th>
<th>Week 9 (± 2 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Physical exam³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>VRC01 administration⁴</strong></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Reactogenicity⁴</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hematology⁵</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td></td>
<td></td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td></td>
<td></td>
<td>0.5 mL</td>
<td></td>
</tr>
<tr>
<td>Chemistries⁶</td>
<td>1 mL</td>
<td>1 mL</td>
<td></td>
<td></td>
<td>1 mL</td>
<td>1 mL</td>
<td></td>
<td></td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td>1 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored urine</td>
<td>3-5 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA PCR⁹</td>
<td>3 mL</td>
<td></td>
<td>3 mL</td>
<td>3 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 mL</td>
<td></td>
</tr>
<tr>
<td>Stored plasma and PBMCs¹⁰</td>
<td>2 mL</td>
<td></td>
<td>2 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 mL</td>
<td></td>
</tr>
<tr>
<td>Stored droplet digital DNA PCR¹¹</td>
<td>3 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored virology DBS¹²</td>
<td>0.25 mL</td>
<td></td>
<td>0.25 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.25 mL</td>
<td></td>
</tr>
<tr>
<td><strong>IMMUNOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored immune responses¹³</td>
<td>X</td>
<td></td>
<td>0.15 mL</td>
<td>0.15 mL</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>RAL¹⁴</td>
<td>X</td>
<td></td>
<td>0.15 mL</td>
<td>0.15 mL</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>VRC01¹⁵</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0 mL</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL BLOOD VOLUME</strong></td>
<td>13.5-15.5 mL</td>
<td>—</td>
<td>1.9 mL</td>
<td>3.15 mL</td>
<td>5.25 mL</td>
<td>—</td>
<td>1.5 mL</td>
<td>1.0 mL</td>
<td>—</td>
<td>6.5 mL</td>
</tr>
</tbody>
</table>
## APPENDIX II-B
### INFANT SCHEDULE OF EVALUATIONS
#### STEP 2 CONTINUED: WEEK 12 THROUGH WEEK 72

<table>
<thead>
<tr>
<th></th>
<th>Weeks 12, 16 &amp; 20 (± 2 wks)</th>
<th>Week 24 (± 2 wks)</th>
<th>Q4 Weeks: Weeks 28, 32, 40, 44, 52, 56, 64, 68 (± 2 wks)</th>
<th>Q12 Weeks: Weeks 36, 48, 60, 72 (± 2 wks)</th>
<th>Premature Discontinuation¹⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical exam³</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology⁶</td>
<td>0-0.5 mL⁷</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistries⁶</td>
<td>0-1 mL⁷</td>
<td>1 mL</td>
<td>1 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td>0-1 mL⁸</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td><strong>Virology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA PCR⁹</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored plasma and PBMCs¹⁰</td>
<td>2 mL¹⁰</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td></td>
</tr>
<tr>
<td>Stored droplet digital DNA PCR¹¹</td>
<td>0-3 mL¹¹a</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td></td>
</tr>
<tr>
<td>Stored virology DBS¹²</td>
<td>0.25 mL</td>
<td></td>
<td>0-0.25 mL¹²a</td>
<td>0.25 mL</td>
<td></td>
</tr>
<tr>
<td><strong>Immunology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored immune responses¹³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0-3 mL¹³a</td>
</tr>
<tr>
<td><strong>Study Agent Concentrations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAL¹⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0-3 mL¹³a</td>
</tr>
<tr>
<td>VRC0¹⁵</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Blood Volume</strong></td>
<td>5-10.5 mL</td>
<td>10.75 mL</td>
<td>—</td>
<td>10.5-13.75 mL</td>
<td>9.25 mL</td>
</tr>
</tbody>
</table>

*May be done in person if preferred by the site (e.g., if participant does not have a phone or in support of visit compliance and/or study regimen adherence).
APPENDIX II-B
STEP 2 ENTRY THROUGH WEEK 72 FOOTNOTES

1. Visit weeks will restart at Week 0 for infants in Step 1 who enter Step 2. Day of Step 2 Entry = Day 0 for this schedule, both for infants who enter Step 2 from Step 1 and for infants who enter Step 2 directly.

2. For infants who enter Step 2 directly, at Entry, history should include sex and race/ethnicity; weight, length, head circumference, and gestational age at birth (based on available medical record documentation); clinical history (diagnoses, signs, symptoms); ARVs and other concomitant medications; interventions for hyperbilirubinemia; method of feeding; and all HIV tests since birth. For infants who enter Step 2 from Step 1, at Entry, and for all infants after Entry, interval history should include clinical history (diagnoses, signs, symptoms); ARVs and other concomitant medications; interventions for hyperbilirubinemia; method of feeding and date of cessation of breastfeeding. All history should be recorded in source documents. The following should be recorded on CRFs: feeding history, all Grade ≥ 3 signs and symptoms, all signs and symptoms (regardless of grade) that lead to a change of study regimen (including any change of any ARV), all diagnoses except those noted on the “do not record” list (available at www.fstrf.org), all HIV tests, all ARVs, all concomitant medications, and all interventions for hyperbilirubinemia.

History at Entry also includes documentation of HIV infection:
- For infants entering Step 2 from Step 1, required HIV testing will be performed as part of Step 1, with results documented prior to entry into Step 2.
- For infants entering Step 2 directly, if documentation of HIV testing meeting requirements in Section 4.3.3 and 6.3.2.2 is not available, blood should be collected for additional testing. At least one positive NAT result must be available prior to entry, and results from a second test meeting protocol requirements must be available within 10 business days after Entry; otherwise, the infant must be discontinued from the study. However, if the second test does not confirm the initial positive result, a third specimen should be collected for a third test selected in consultation with the CMC, with the result available within 10 additional business days. At least one of the first two tests must be performed at a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory. If performed, the third test must also be performed at a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory.

3. Physical exam includes temperature, heart rate, respiratory rate, weight, length, head circumference, breath sounds, heart sounds; additionally at Entry for infants who enter Step 2 directly, examination of skin, head, mouth, neck, abdomen, extremities; additionally after Entry: examination of body systems driven by prior and new signs, symptoms, and diagnoses. For infants receiving Regimen 2RV, VRC01 injection sites will also be examined through Week 9.

4. Infants receiving Regimen 2RV will be administered VRC01 at Entry, Week 4, and Week 8. The Week 8 visit and the 3-day contacts following the Entry, Week 4, and Week 8 visits are required only for infants receiving this regimen. Per Section Reactogenicity Monitoring for Infants Receiving VRC01, infants receiving this regimen will be monitored for reactogenicity by site clinicians following each administration of VRC01. Infant caregivers will also be instructed to complete memory aid documents to record infant signs and symptoms for seven days (beginning on the day of each administration). Three days after each administration, caregivers will be contacted by study staff to report their reactogenicity assessments; seven days after administration (i.e., at the Week 1, Week 5, and Week 9 visits), caregivers will again report their assessments.

5. Hematology: Complete blood count with differential and platelet count.

6. Chemistries:
- For infants receiving Regimen 1L: AST, ALT, lipase, and glucose at all indicated time points.
- For infants receiving Regimen 2R or 2RV: AST, ALT, ALP, and creatinine at all indicated time points; total bilirubin only at Entry and Week 2.

7. Perform hematology and chemistries at Week 16 only (not required at Weeks 12 and 20).
8. Perform CD4 count at Week 12 only (not required at Weeks 16 and 20).
9. Must be performed in real time at a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory.
10. Samples will be stored for future testing to identify host and viral factors associated with HIV remission, including HIV drug and VRC01 resistance testing, viral sequencing, and if remission is achieved, HIV DNA/TNA quantification to identify the time point when the virus was cleared. Samples collected at Entry, Week 4, Week 16, and Week 24 will also have HIV DNA/TNA PCR testing performed. Samples may be used for droplet digital DNA PCR. If needed for clinical or ARV regimen management, in consultation with the CMC, samples may additionally be collected at time points not indicated in the table for resistance testing. For infants receiving Regimen 2RV, at Entry and Week 4, samples must be collected prior to administration of VRC01.
11. Droplet digital HIV DNA PCR will be used as additional testing for HIV persistence and for future evaluation of children in remission.
   a. Collect at Week 12 only.
12. Virology DBS will be used for future viral sequencing and to evaluate host and viral factors associated with HIV remission. At premature discontinuation, virology DBS will be used for HIV RNA level.
   a. Collect at Week 48 and Week 72 only.
13. Sample will be used to evaluate infant immune responses. At labs that participate in the IQA cryopreservation proficiency testing program and are able to store samples in LN2 or at -150 C prior to shipment, plasma and viably cryopreserved PBMC will be stored.
   a. Collect at Week 72 only
14. At Step 2 Entry and Week 4, for infants receiving Regimen 2R or Regimen 2RV, plasma aliquots for RAL concentrations will be obtained from the 2 mL of blood collected for plasma and PBMC storage. At Weeks 1 and 2, collect samples for RAL concentration.
15. At Step 2 Entry and Weeks 4, 12, 16, 20, and 24, for infants receiving Regimen 2RV, plasma aliquots for VRC01 concentrations will be obtained from the 2 mL of blood collected for plasma and PBMC storage. At Week 8, collect sample for VRC01 concentration. At Step 2 Entry, Week 4, and Week 8, samples must be collected prior to administration of VRC01.
16. See Section Premature Discontinuation from Study Follow-up for criteria for premature discontinuation from the study.

Unless otherwise specified, all stored samples are retained locally until requested by the team for shipment to the repository or the designated centralized testing laboratory for batched testing.

NIH recommended pediatric blood collection limits of 5 mL/kg in a single day and 9.5 mL/kg in any 8-week period should be followed. Refer to the blood draw priority list below. All sites should comply with IRB/EC limitations.

**Blood draw priority lists**

<table>
<thead>
<tr>
<th>Entry through Week 20</th>
<th>Week 24 through Week 72</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Virology (except stored samples [see #6 below])</td>
<td>1. Virology (except stored samples [see #6 below])</td>
</tr>
<tr>
<td>2. Hematology</td>
<td>2. CD4</td>
</tr>
<tr>
<td>3. Chemistries</td>
<td>3. Study agent concentrations</td>
</tr>
<tr>
<td>4. CD4</td>
<td>4. Hematology</td>
</tr>
<tr>
<td>5. Study agent concentrations</td>
<td>5. Chemistries</td>
</tr>
<tr>
<td>6. Stored samples</td>
<td>6. Stored samples</td>
</tr>
</tbody>
</table>
## APPENDIX II-C

### INFANT SCHEDULE OF EVALUATIONS

#### STEP 2 ART CESSION EVALUATION VISITS* – WEEK 84 THROUGH WEEK 192

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History¹</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical exam²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology³,⁴</td>
<td>0.5 mL</td>
<td>0-0.5 mL</td>
<td>0.5 mL</td>
<td>0-0.5 mL</td>
<td>0.5 mL</td>
<td>0-0.5 mL</td>
<td>0.5 mL</td>
<td>0-0.5 mL</td>
<td>0.5 mL</td>
<td>0-0.5 mL</td>
<td>0-0.5 mL</td>
</tr>
<tr>
<td>Chemistries⁵</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>CD4⁴</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
</tr>
<tr>
<td><strong>VIROLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA PCR⁶</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td></td>
</tr>
<tr>
<td>HIV-1 antibody⁷</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>Stored droplet digital HIV DNA PCR⁸</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td></td>
</tr>
<tr>
<td>Replication-competent virus and single copy HIV RNA⁹</td>
<td>9 mL</td>
<td>9 mL</td>
<td>9 mL</td>
<td>9 mL</td>
<td>9 mL</td>
<td>9 mL</td>
<td>9 mL</td>
<td>9 mL</td>
<td>9 mL</td>
<td>9 mL</td>
<td></td>
</tr>
<tr>
<td>Stored plasma and PBMC¹⁰</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td></td>
</tr>
<tr>
<td>Stored virology DBS¹¹</td>
<td>0.25 mL</td>
<td>0.25 mL</td>
<td>0.25 mL</td>
<td>0.25 mL</td>
<td>0.25 mL</td>
<td>0.25 mL</td>
<td>0.25 mL</td>
<td>0.25 mL</td>
<td>0.25 mL</td>
<td>0.25 mL</td>
<td></td>
</tr>
<tr>
<td><strong>IMMUNOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored responses¹²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 mL</td>
</tr>
<tr>
<td><strong>TOTAL BLOOD VOLUME</strong></td>
<td>11.5 mL</td>
<td>17.25-17.75 mL</td>
<td>11.5 mL</td>
<td>17.25-17.75 mL</td>
<td>11.5 mL</td>
<td>17.25-17.75 mL</td>
<td>11.5 mL</td>
<td>17.25-17.75 mL</td>
<td>14.5 mL</td>
<td>17.25-17.75 mL</td>
<td>6.0-6.5 mL</td>
</tr>
</tbody>
</table>

Day of Step 2 Entry = Day 0 for this schedule.
APPENDIX II-C
STEP 2 WEEK 84 THROUGH WEEK 192 FOOTNOTES

* Beginning at Week 84, infants will be evaluated for eligibility to move to Step 3 (ART cessation). See Section 4.4 for the Step 3 inclusion criteria and Section 6.3.2.4 for the evaluation procedure. Infants meeting the inclusion criteria will enter Step 3 (APPENDIX II-D) as soon as possible after the criteria have been met.

1. Interval history should include clinical history (diagnoses, signs, symptoms); ARVs and other concomitant medications; method of feeding and date of cessation of breastfeeding. All history should be recorded in source documents. The following should be recorded on CRFs: feeding history, all Grade ≥ 3 signs and symptoms, all signs and symptoms (regardless of grade) that lead to a change of study regimen (including any change of any ARV), all diagnoses except those noted on the “do not record” list (available at www.fstrf.org), all ARVs, and all concomitant medications.

2. Physical exam includes temperature, heart rate, respiratory rate, weight, length, head circumference, breath sounds, heart sounds, and examination of body systems driven by prior and new signs, symptoms, and diagnoses.

3. Hematology: Complete blood count with differential and platelet count.

4. At sites where a complete blood count is needed to obtain CD4 cell counts and percentages, 0.5 mL of blood may be collected to perform the complete blood count at weeks when CD4 testing is required but hematology testing is not otherwise required.

5. Chemistries:
   - For infants receiving Regimen 1L: AST, ALT, lipase, and glucose.
   - For infants receiving Regimen 2R or 2RV: AST, ALT, ALP, and creatinine.

IMPORTANT INSTRUCTION for virology evaluations and footnotes 6-11: Following permanent cessation of breastfeeding (if applicable) and a first negative HIV-1 antibody test result, virology specimens will be shipped for testing at designated central laboratories to assess eligibility for Step 3. Contact the Protocol Team to confirm samples to be shipped and discuss shipping details prior to shipment.

6. Must be performed in real time at a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory. Save extra plasma for fourth generation ELISA and Western blot.

7. HIV-1 antibody by ELISA or rapid test performed locally in real time.

8. Droplet digital DNA PCR will be used as additional testing for HIV persistence and for future evaluation of children in remission.

9. Replication-competent virus sample will be used for additional testing for HIV persistence and single copy HIV RNA. If cell volume is insufficient, alternate assays (e.g., TILDA) may be performed. Samples will be processed in real-time with overnight shipment for US sites. For non-US sites, samples will be cryopreserved for shipment in batch.
APPENDIX II-C
FOOTNOTES

STEP 2 (cont’d): INFECTED INFANTS IN COHORT 1 AND COHORT 2
ART CESSATION EVALUATION VISITS* – WEEK 84 THROUGH WEEK 192

10. Sample will be stored for future testing to identify host and viral factors associated with HIV remission, including HIV drug and VRC01 resistance testing, viral sequencing, and, if remission is achieved, HIV DNA/TNA quantification to identify the time point when the virus was cleared. If needed for clinical or ARV regimen management, in consultation with the CMC, samples may additionally be collected at time points not indicated in the table for resistance testing.

11. Virology DBS will be used for future viral sequencing and to evaluate host and viral factors associated with HIV remission.

12. Sample will be used to evaluate infant immune responses. At labs that participate in the IQA cryopreservation proficiency testing program and are able to store samples in LN2 or at -150 C prior to shipment, plasma and viably cryopreserved PBMC will be stored.

13. See Section Premature Discontinuation from Study Follow-up for criteria for premature discontinuation from the study.

Unless otherwise specified, all stored samples are retained locally until requested by the team for shipment to the repository or the designated centralized testing laboratory for batched testing.

NIH recommended pediatric blood collection limits of 5 mL/kg in a single day and 9.5 mL/kg in any 8-week period should be followed. Refer to the blood draw priority list below. All sites should comply with IRB/EC limitations.

Blood draw priority list
1. Virology (except stored plasma and PBMC, see #6 below) – if insufficient blood draw, do not collect replication-competent virus sample
2. CD4
3. Hematology
4. Chemistries
5. Immunology
6. Stored Plasma and PBMC
APPENDIX II-D
SCHEDULE OF EVALUATIONS
STEP 3: ART CESSIONATION

Entry through Week 12

<table>
<thead>
<tr>
<th></th>
<th>Step 3 Entry¹</th>
<th>Week 1 (± 2 days)</th>
<th>Week 2 (± 2 days)</th>
<th>Week 3 (± 2 days)</th>
<th>Week 4 (± 2 days)</th>
<th>Week 6 (± 1 wk)</th>
<th>Week 8 (± 1 wk)</th>
<th>Week 12 (± 2 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discussion of Step 3 entry and ART cessation in the context of latest scientific updates, informed consent¹</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical exam³</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4⁴</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 mL</td>
</tr>
<tr>
<td><strong>VIROLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA⁵</td>
<td>3 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
</tr>
<tr>
<td>Stored HIV DNA/TNA PCR⁶</td>
<td>2 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored droplet digital HIV DNA PCR⁷</td>
<td>3 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored single copy HIV RNA⁸</td>
<td>5 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 mL</td>
<td></td>
</tr>
<tr>
<td>Replication-competent virus⁹</td>
<td>0-9 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored plasma and PBMC¹⁰</td>
<td></td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IMMUNOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored immune responses¹¹</td>
<td>3 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL BLOOD VOLUME</strong></td>
<td>17-26 mL</td>
<td>1.5 mL</td>
<td>4.5 mL</td>
<td>1.5 mL</td>
<td>10.5 mL</td>
<td>1.5 mL</td>
<td>4.5 mL</td>
<td>2.5 mL</td>
</tr>
</tbody>
</table>
## APPENDIX II-D
### SCHEDULE OF EVALUATIONS
### STEP 3 (cont’d.): ART CESSION

**APPENDIX II-D**
**SCHEDULE OF EVALUATIONS**
**STEP 3 (cont’d.): ART CESSION**

**Week 16 through Week 48**

<table>
<thead>
<tr>
<th></th>
<th>Week 16 (± 1 wk)</th>
<th>Week 20 (± 1 wk)</th>
<th>Week 24 (± 2 wks)</th>
<th>Week 28 (± 2 wks)</th>
<th>Week 32 (± 2 wks)</th>
<th>Week 36 (± 2 wks)</th>
<th>Week 40 (± 2 wks)</th>
<th>Week 44 (± 2 wks)</th>
<th>Week 48 (± 2 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td></td>
<td></td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
</tr>
<tr>
<td>HIV RNA</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
</tr>
<tr>
<td><strong>VIROLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored HIV DNA/TNA PCR</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
</tr>
<tr>
<td>Stored droplet digital HIV DNA PCR</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
</tr>
<tr>
<td>Stored single copy HIV RNA</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
</tr>
<tr>
<td>Replication-competent virus</td>
<td>9 mL</td>
<td>9 mL</td>
<td>9 mL</td>
<td>9 mL</td>
<td>9 mL</td>
<td>9 mL</td>
<td>9 mL</td>
<td>9 mL</td>
<td>9 mL</td>
</tr>
<tr>
<td>Stored plasma and PBMC</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
</tr>
<tr>
<td><strong>IMMUNOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored responses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL BLOOD VOLUME</strong></td>
<td>14.5 mL</td>
<td>1.5 mL</td>
<td>27.5 mL</td>
<td>1.5 mL</td>
<td>15.5 mL</td>
<td>1.5 mL</td>
<td>7.5 mL</td>
<td>1.5 mL</td>
<td>27.5 mL</td>
</tr>
</tbody>
</table>
### APPENDIX II-D
### SCHEDULE OF EVALUATIONS
### STEP 3 (cont’d.): ART CESSION

#### Week 52 through Week 240

|                              | Q4 Weeks (± 2 wks) | Q12 Weeks (± 2 wks) | Premature Discontinuation
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History²</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical exam³</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4⁴</td>
<td></td>
<td>1 mL</td>
<td>0-1 mL</td>
</tr>
<tr>
<td><strong>Virology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA⁵</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
<td>1.5 mL</td>
</tr>
<tr>
<td>Stored HIV DNA/TNA PCR⁶</td>
<td></td>
<td>2 mL</td>
<td>2 mL</td>
</tr>
<tr>
<td>Stored droplet digital HIV DNA PCR⁷</td>
<td></td>
<td>3 mL</td>
<td></td>
</tr>
<tr>
<td>Stored single copy HIV RNA⁸</td>
<td></td>
<td>5 mL</td>
<td></td>
</tr>
<tr>
<td>Replication-competent virus⁹</td>
<td></td>
<td>0-9 mL⁹a</td>
<td></td>
</tr>
<tr>
<td>Stored plasma and PBMC¹⁰</td>
<td></td>
<td>3 mL</td>
<td>3 mL</td>
</tr>
<tr>
<td><strong>Immunology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored immune responses¹¹</td>
<td></td>
<td>0-3 mL¹¹a</td>
<td></td>
</tr>
<tr>
<td><strong>Total Blood Volume</strong></td>
<td>1.5 mL</td>
<td>15.5-27.5 mL</td>
<td>6.5-7.5 mL</td>
</tr>
</tbody>
</table>
APPENDIX II-D
FOOTNOTES
STEP 3: ART CESSION

1. Discussion of Step 3 entry and ART cessation in the context of latest scientific updates, followed by obtaining written informed consent, must occur prior to entry into Step 3 (see Section Evaluation to Determine Eligibility for Treatment Cessation). Visit weeks will restart at Week 0 on entry into Step 3 (day of Step 3 Entry = Day 0). ART will be discontinued after blood collection at Step 3 Entry.
2. Interval history (at Step 3 Entry, history from the last visit in Step 2) should include clinical history (diagnoses, signs, symptoms), ARVs between the last Step 2 visit and the Step 3 Entry visit, and concomitant medications. All history should be recorded in source documents. The following should be recorded on CRFs: all Grade ≥ 3 signs and symptoms, all diagnoses except those noted on the “do not record” list (available at www.fstrf.org), ARVs between the last Step 2 visit and the Step 3 Entry visit, and all concomitant medications.
3. Physical exam includes temperature, heart rate, respiratory rate, weight, length, head circumference, breath sounds, heart sounds, and examination of body systems driven by prior and new signs, symptoms, and diagnoses.
4. At sites where a complete blood count is needed to obtain CD4 cell counts and percentages, an additional 0.5 mL of blood may be collected to perform a CBC. This test is not required at Premature Discontinuation if the prior test done was within 12 weeks of the visit.
5. At Entry, perform a standard quantitative HIV RNA assay at a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory. After Entry, perform on-demand assays with diluted plasma following the laboratory’s validated dilution plan. Refer to the LPC for assay and dilution requirements. If an on-demand assay yields a positive result, collect an additional 3 mL of blood as soon as possible and within 72 hours to perform a standard quantitative HIV RNA assay with undiluted plasma at a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory; the standard quantitative HIV RNA assay should be performed as soon as possible and within 96 hours of specimen collection. Store all residual samples. 5a. If HIV RNA testing is not performed within the Week 48 visit window for any reason, the child should be recalled to the clinical as soon as possible for testing performed as part of the Week 52 visit.
6. Sample will be stored for future testing.
7. Droplet digital HIV DNA PCR sample will be used for additional testing for HIV persistence and for future evaluation of children in remission.
8. Sample will be stored for future evaluation of children in remission.
9. Replication-competent virus sample will be used for additional testing for viral persistence. Sample at Entry is not required if a sample was collected in Step 2 within 30 days of the visit. If cell volume is insufficient, alternate assays (e.g., TILDA) may be performed. For US sites, samples will be processed in real-time with overnight shipment. For non-US sites, samples will be cryopreserved for shipment in batch. a. Beginning at Week 72, collect every 24 weeks.
10. Stored samples for future testing to identify host and viral factors associated with HIV remission, including HIV drug and VRC01 resistance testing, viral sequencing, and if remission is achieved, HIV DNA/TNA quantification to identify the time point when the virus was cleared. Samples may also be tested for evidence of ARV use at a central pharmacology laboratory.
APPENDIX II-D
FOOTNOTES
STEP 3: ART CESSIONATION

11. Sample will be used to evaluate infant immune responses. At labs that participate in the IQA cryopreservation proficiency testing program and are able to store samples in LN2 or at -150 C prior to shipment, plasma and viably cryopreserved PBMC will be stored.
   a. Beginning at Week 60, collect every 24 weeks.
12. See Section Premature Discontinuation from Study Follow-up for criteria for premature discontinuation from the study.

Unless otherwise specified, all stored samples are retained locally until requested by the team for shipment to the repository or the designated centralized testing laboratory for batched testing.

NIH recommended pediatric blood collection limits of 5 mL/kg in a single day and 9.5 mL/kg in any 8-week period should be followed. Refer to the blood draw priority list below. All sites should comply with IRB/EC limitations.

**Blood draw priority list**
1. Virology
2. CD4
3. Immunology
## APPENDIX II-E
### SCHEDULE OF EVALUATIONS
#### STEP 4 – ART RE-INITIATION

<table>
<thead>
<tr>
<th></th>
<th>Step 4 Entry</th>
<th>Week 1 (±2 days) by phone contact</th>
<th>Week 2 (±2 days) by phone contact</th>
<th>Week 3 (±2 days)</th>
<th>Week 4 (±1 wk)</th>
<th>Week 6 (±1 wk)</th>
<th>Week 8 (±1 wk)</th>
<th>Week 10 (±1 wk)</th>
<th>Week 12 until viral suppression (±1 wk)</th>
<th>Week 16 then q4 weeks until viral suppression (±1 wk)</th>
<th>Week 24 then q12 weeks (± 6 wks)*</th>
<th>Premature Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Physical exam³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology⁴</td>
<td>0.5 mL</td>
<td></td>
<td></td>
<td>0.5 mL</td>
<td></td>
<td></td>
<td></td>
<td>0.5 mL</td>
<td>0.5 mL⁴a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistries⁵</td>
<td>1 mL</td>
<td></td>
<td></td>
<td>1 mL</td>
<td></td>
<td></td>
<td></td>
<td>1 mL</td>
<td>0-1 mL⁵a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td>1 mL</td>
<td></td>
<td></td>
<td>1 mL</td>
<td></td>
<td></td>
<td></td>
<td>1 mL</td>
<td>1 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Virology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA PCR⁶</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored resistance testing⁷</td>
<td>2 mL⁷a</td>
<td></td>
<td></td>
<td>0-2 mL⁷b</td>
<td>0-2 mL⁷b</td>
<td>0-2 mL⁷b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored droplet digital DNA PCR⁸</td>
<td>3 mL</td>
<td></td>
<td></td>
<td>3 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Replication-competent virus⁹</td>
<td>3 mL</td>
<td></td>
<td></td>
<td>3 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored virology DBS¹⁰</td>
<td>0.25 mL</td>
<td></td>
<td></td>
<td>0.25 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immunology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored immune responses¹¹</td>
<td>3 mL</td>
<td></td>
<td></td>
<td>3 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Blood Volume</strong></td>
<td>10.75 mL</td>
<td>3 mL</td>
<td>4.5 mL</td>
<td>6 mL</td>
<td>3 mL</td>
<td>3-5 mL</td>
<td>8.75-10.75 mL</td>
<td>3 mL</td>
<td>16.25-20.75 mL</td>
<td>4-6 mL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Children who experience viral rebound in Step 3 will enter Step 4 and be followed in Step 4 through 5 years of age or until 6 months after viral re-suppression on ART, whichever is later.
APPENDIX II-E
FOOTNOTES
STEP 4 – ART RE-INITIATION

1. Visit weeks will restart at Week 0 on entry into Step 4 (day of Step 4 Entry = Day 0).
2. Interval history (at Step 4 Entry, history since the last visit in Step 3) should include clinical history (diagnoses, signs, symptoms), ARVs and other concomitant medications. All history should be recorded in source documents. The following should be recorded on CRFs: all Grade ≥ 3 signs and symptoms, all signs and symptoms (regardless of grade) that lead to a change of ARV regimen (including any change of any ARV), all diagnoses except those noted on the “do not record” list (available at www.fstrf.org), all ARVs, and all concomitant medications.
3. Physical exam includes temperature, heart rate, respiratory rate, weight, length, head circumference, breath sounds, heart sounds, and examination of body systems driven by prior and new signs, symptoms, and diagnoses.
   a. Perform every 24 weeks beginning at Week 24.
5. Chemistries:
   • For infants receiving Regimen 1L: AST, ALT, lipase, and glucose.
   • For infants receiving Regimen 2R or 2RV: AST, ALT, ALP, and creatinine.
   a. Perform every 24 weeks beginning at Week 24.
6. Must be performed in real time at a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory.
7. Sample will be stored for future testing.
   a. Sample collected at Entry will be stored for later testing if viral re-suppression does not occur after ART re-initiation.
   b. Collect sample if HIV RNA is > 1,000 copies/mL at the previous visit (if done at Week 10, do not repeat at Week 12). Test should be run at a local laboratory if there is capability. If the local laboratory is unable to perform the test, sample will be shipped in real time to a designated regional or central laboratory.
8. Droplet digital DNA PCR sample will be used for additional testing for HIV persistence.
9. Replication-competent virus sample will be used for additional testing for viral persistence. If cell volume is insufficient, alternate assays (e.g., TILDA) may be performed. Samples will be processed in real-time with overnight shipment for US sites. For non-US sites, samples will be cryopreserved for shipment in batch.
   a. Beginning at Week 48, collect every 24 weeks.
10. Virology DBS will be used for future studies of viral sequencing.
APPENDIX II-E
FOOTNOTES
STEP 4 – ART RE-INITIATION

11. Sample will be used to evaluate infant immune responses. At labs that participate in the IQA cryopreservation proficiency testing program and are able to store samples in LN2 or at -150 C prior to shipment, plasma and viably cryopreserved PBMC will be stored.
   a. Beginning at Week 48, collect every 48 weeks.
12. If HIV RNA PCR is not < LOD at Week 12, conduct study visits every four weeks for continued monitoring of viral load. At these visits, history (including adherence to ARV regimen) should also be evaluated. Once HIV RNA PCR is < LOD, continue with study visits every 12 weeks. 
13. See Section Premature Discontinuation from Study Follow-up for criteria for premature discontinuation from the study.

Unless otherwise specified, all stored samples are retained locally until requested by the team for shipment to the repository or the designated centralized testing laboratory for batched testing.

NIH recommended pediatric blood collection limits of 5 mL/kg in a single day and 9.5 mL/kg in any 8-week period should be followed. Refer to the blood draw priority list below. All sites should comply with IRB/EC limitations.

Blood draw priority list
1. Virology
2. CD4
3. Immunology
4. Hematology
5. Chemistry
# APPENDIX III

## SUPPLEMENTAL TOXICITY TABLE FOR GRADING SEVERITY OF CUTANEOUS/SKIN RASH/DERMATITIS ADVERSE EVENTS

<table>
<thead>
<tr>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CUTANEOUS/SKIN RASH/DERMATITIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Erythema, with or without pruritus | 2A. Diffuse erythematous macular or maculopapular cutaneous eruption or dry desquamation with or without pruritus (without the presence of any additional constitutional findings as described in Grade 3 of DAIDS AE Grading Table) | A. Diffuse erythematous macular or maculopapular cutaneous eruption or moist desquamation with or without pruritus together with any of the following constitutional findings considered related to study drug:  
- 5 x ULN AST, ALT or 2 x baseline if baseline > ULN  
- fever, > 39°C  
- blistering and/or vesiculation of cutaneous eruptions  
- any site of mucosal lesions; OR  
B. angioedema; OR  
C. exfoliative dermatitis defined as severe widespread erythema and dry scaling of the skin, with generalized superficial lymphadenopathy, and with other constitutional findings such as fever, weight loss, hypoproteinemia possibly related to study drug; OR  
D. diffuse rash and serum sickness-like reactions defined as a clinical symptom complex manifested as fever, lymphadenopathy, edema, myalgia, and/or arthralgia; OR  
E. diffuse cutaneous eruptions, usually starting on the face, trunk or back, often with prodromal symptoms plus one of the following:  
1. cutaneous bullae, sometimes confluent with widespread sheet-like detachment of skin (< 10% body surface area), (Nikolsky's sign), (Stevens Johnson Syndrome, SJS)  
2. two or more anatomically distinct sites of mucosal erosion or ulceration not due to another cause | Diffuse cutaneous eruptions, usually starting on the face, trunk or back, often with prodromal symptoms plus cutaneous bullae with widespread sheet-like detachment of skin (>10% of body surface area), (Nikolsky's sign), (SJS/Toxic Epidermal Necrolysis (TEN) overlap syndrome; TEN) |
| 2B. Urticaria OR typical target lesions without blistering, vesicles, or ulcerations in the lesions. | | | |

For all Grade 3 and 4 cutaneous/skin rash/dermatitis adverse experiences, photo documentation of the rash is strongly recommended.
INTRODUCTION
You are being asked to allow your baby to take part in this research study because you have tested positive for the Human Immunodeficiency Virus (HIV), the virus that causes AIDS, and your baby may be infected with HIV. This study is sponsored by the United States National Institutes of Health. The doctor in charge of this study at this site is: (insert name of Investigator of Record). Before you decide if you want your baby to participate, we want you to know about the study.

This is a consent form. It gives information about the study. The study staff will talk with you about this information. You are free to ask questions at any time. If you allow your baby to take part in the study, you will be asked to sign this form. You will be offered a copy to keep.

WHY IS THIS STUDY BEING DONE?
The main purpose of this study is to find out if starting anti-HIV medicines (ARVs) within 48 hours of birth can make it possible for babies who are infected with HIV to control HIV so well that HIV cannot be detected in their blood. As of now, when children with HIV start taking ARVs, they usually need to keep taking them for life. For newborn babies who start ARVs very soon after birth, it might be possible to later stop taking ARVs for a prolonged period of time and still stay healthy. This has only been seen in one child so far. That child started ARVs soon after birth, then stopped ARVs and was able to stay healthy, with no HIV detected in the blood for more than 2 years. About 27 months after stopping ARVs, HIV was detected in this child’s blood, and the child restarted ARVs. The amount of HIV in the child’s blood quickly dropped, and the child has remained healthy. This study is being done to find out if this can be seen in other babies who start ARVs very soon after birth. This study is also looking at the levels of ARVs that are safe and work well for babies this young.

WHAT DOES YOUR BABY HAVE TO DO AS PART OF THIS STUDY?
This study has four steps. At this time, you are being asked to allow your baby to take part only in Step 1. This step is for babies whose mothers have HIV and it is not yet known if the babies have HIV. The study will do testing to confirm if your baby has HIV.

- If your baby DOES NOT have HIV, he or she will be in Step 1 of the study for 12 weeks.
- If your baby DOES have HIV, you will be asked to allow your baby to take part in Step 2 of the study. Step 2 will be explained to you and you will be asked to sign another consent form for that step. An information sheet about Steps 2, 3, and 4 is attached to this form.

The rest of this form explains Step 1, which involves five visits. If you allow your baby to take part, the Entry Visit will continue today. The other visits will be in 1, 2, 4, and 12 weeks. The Entry Visit will take about 4 hours. The other visits will take 1-2 hours.
At the Entry Visit

- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have about 2 teaspoons (10 mL) of blood drawn for:
  - Tests for HIV infection and the amount of HIV in the blood. For these tests, blood will be drawn two times, at least one hour apart, within the first 48 hours of birth.
  - Routine safety tests. These tests check for problems with your baby’s blood cells, liver, and kidneys, which can sometimes be side effects of ARVs.
  - Other HIV-related tests.
- Your baby will take ARVs. The ARVs may include raltegravir, nevirapine, and other ARVs chosen by the study doctor. The study staff will tell you about the ARVs and how to give them to your baby. Some ARVs will be given as part of the study. The study staff will explain where to obtain the other ARVs and whether your insurance will need to pay for them. [Note to sites: This paragraph may be modified to reflect usual ARV prescribing and dispensing practices at your site; please note, however that the ARVs provided in this step, other than raltegravir are not study-supplied and should be obtained from non-study sources.]

At the Week 1 and Week 2 Visits

- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have less than 1 teaspoon (less than 5 mL) of blood drawn for safety tests and HIV-related tests. Tests of the amount of ARVs in the blood will also be done.

The results of your baby’s first tests for HIV infection will be known by the time of the Week 2 visit.

If your baby has HIV, Step 2 of the study will be explained to you and you will be asked to sign another consent form for that step. If you agree, your baby will enter Step 2.

If your baby does not have HIV, the ARVs started at the Entry Visit will be stopped and ARVs usually given to prevent babies from getting HIV will be given instead. The study staff will explain this change to you. Your baby will have two more visits (described below) and then will leave the study.

At the Week 4 Visit

- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have less than 1 teaspoon (less than 5 mL) of blood drawn only if the safety tests done at Week 2 showed abnormal results. Otherwise no blood will be collected.
- The study staff will refer you to other sources of care for your baby outside the study, including sources of ARVs and HIV testing. Even though your baby was not found to have HIV in this study, he or she could still test positive later. It is important that he or she be tested again at 6-10 weeks of age.

At the Week 12 Visit

- You will be asked about whether your baby had any HIV tests since the Week 4 visit.
- Your baby will have less than 1 teaspoon (less than 5 mL) of blood drawn for tests for HIV infection and other HIV-related tests.
- The study staff will tell you how the get the results of your baby’s HIV test. As needed, they will also talk with you again other sources of care for your baby outside the study.
GENETIC TESTING
Some of the blood tests done for this study will look at how your baby’s genes (DNA) affect his or her response to HIV and ARVs. The researchers will not contact you or your baby’s regular health care provider with the results of these tests. This is because these tests are often done with experimental procedures and the results should not be used to make decisions about your baby’s health care. However, if the researchers decide that a result is important for your baby’s health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your baby’s blood used for genetic testing. Your baby can still be in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my baby’s blood to be used for genetic testing as part of this study.

__________ Yes __________ No __________ Date

STORAGE OF BLOOD FOR FUTURE USE
After the tests planned to be done for this study are completed, some of your baby’s blood may be leftover. The IMPAACT Network would like to keep this blood for other research in the future. If you agree to this, your baby’s leftover blood samples will be stored and tested at special laboratory facilities that may be in the US and other countries outside of [insert site country]. Only approved researchers will have access to them. People who work at the facilities will also have access to your baby’s samples to keep track of them. These people won’t have information that directly identifies your baby. Your baby’s samples will not be sold or directly used to produce commercial products. All proposed research studies using your baby’s samples will be reviewed by the IMPAACT Network. There is no time limit on how long your baby’s samples will be stored.

The researchers will not contact you or your baby’s regular health care provider with the results of future research tests. This is because research tests are often done with experimental procedures and the results should not be used to make decisions about your baby’s health care. However, if the researchers decide that a result is important for your baby’s health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your baby’s leftover samples stored for future research. Your baby can still be in this study even if you make this decision. You may also withdraw consent for storage and future use of your baby’s samples at any time. If you withdraw your consent, the leftover samples will be destroyed.

Please read the following statements carefully and then mark your initials in the appropriate space provided.

I allow my baby’s leftover blood samples to be stored for use in future IMPAACT-approved, HIV-related research studies.

__________ Yes __________ No __________ Date
I allow my baby’s leftover blood samples to be used for genetic testing as part of future IMPAACT-approved, HIV-related research studies.

__________ Yes  __________ No  __________ Date

**HOW MANY BABIES WILL BE IN THIS STUDY?**
About 450 babies have already taken part in Step 1 of this study. Another 450, for a total of 900, are expected to take part.

**HOW LONG WILL BABIES BE IN THIS STUDY?**
Babies will be in Step 1 of the study for 12 weeks.

**WHY WOULD THE DOCTOR TAKE YOUR BABY OFF THIS STUDY EARLY?**
The study doctor may need to take your baby off Step 1 of this study early without your permission for the reasons listed below. If this happens, no further information will be collected, and no further study visits or laboratory tests will be done.

- You do not have HIV infection.
- Your baby stops coming to the clinic for study visits.
- The study doctor determines that further participation would be harmful to your baby’s health or well-being.
- The study is stopped or cancelled.

**WHAT ARE THE RISKS OF THE STUDY?**
Blood drawing may cause some discomfort, bleeding, or bruising where the needle enters the body. A small blood clot may form at the site where the blood was drawn or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur.

Babies in Step 1 of this study will be given four ARVs. The ARVs will be started earlier than usual (before a baby is known to have HIV). Also, nevirapine will be given at a higher dose than usual. This dosing may have more side effects. For example, the ARVs could cause low blood cells.

Some of the possible side effects of raltegravir and nevirapine are listed below. These are the serious or common side effects that have a known or possible relationship with these ARVs. These are not complete lists of all side effects. The study staff will discuss these with you. They will also tell you about the side effects of other ARVs your baby will be given. Please ask the study staff any questions you may have about ARVs and their possible side effects. Please also contact the study staff with any concerns about your baby’s health and possible side effects.

**Raltegravir, (RAL, Isentress™)**
Merck Research Laboratories

The following side effects have been associated with raltegravir:

- Rash which can become severe or life-threatening. Contact the study staff right away if your baby develops a rash.
- Headache
- Nausea
- Stomach pain and diarrhea
• Tiredness
• Trouble sleeping
• Dizziness
• Depression, including suicidal thoughts and actions
• Feeling anxious, paranoia
• Changes in behavior, like low or high activity in children
• Clumsiness and lack of coordination
• Easy bleeding (decreased blood clotting, low platelet count)
• Muscle tenderness, weakness or injury which can be serious and lead to kidney damage

Hypersensitivity or “allergic” reactions may occur. These reactions can cause some of the symptoms listed above. They can also affect body organs such as the liver. If the liver is affected, this can be severe. Contact the study staff if your baby has signs of liver problems. These signs include:

• Yellowing of the skin or whites of the eyes
• Dark urine
• Pale stools
• Loss of appetite
• Nausea or vomiting
• Pain, aching, or tenderness on the right side below the ribs
• Tiredness or general feeling of illness

**Nevirapine (NVP)**
The following serious side effects have been associated with nevirapine:

Severe liver damage that can result in death may occur and is often associated with a rash. People with abnormal liver function tests before starting nevirapine and people with active Hepatitis B or C infection are at higher risk for liver damage. Contact the study staff if your baby has signs of liver problems. These signs are listed above.

Hypersensitivity or “allergic” reactions may occur. These reactions are rarely fatal. The symptoms that your baby may have are rash, fever, tiredness, muscle or joint aches, flu-like feeling, blisters, mouth sores, facial swelling, red eyes and irritation of the eyes, general feeling of discomfort, and/or liver damage described above, kidney problems, and/or changes in white blood cell levels.

Muscle break down causing muscle aches or pain has been observed in some people experiencing skin and/or liver reactions associated with nevirapine.

Rash is the most common side effect associated with nevirapine. Most rashes occur early during treatment. The rash may be severe and rarely may cause death.

The risk of developing any of the serious side effects listed above is greatest during the first few months of treatment, but these side effects also can occur later. If your baby develops any of the side effects listed above, no matter how long he or she has been receiving nevirapine, you must contact the study staff right away and before you give your baby the next dose. The study doctor will instruct you on what to do next. If you and your doctor then decide to stop your baby’s treatment because of liver damage, hypersensitivity or severe skin reactions, your baby should never take nevirapine again.
In addition to the serious side effects listed above, additional side effects include:

- Fever
- Headache
- Upset stomach (nausea, vomiting)

**ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?**
This study may be of no direct benefit to your baby. Information learned from this study may help others who have HIV.

**WHAT OTHER CHOICES DOES YOUR BABY HAVE BESIDES THIS STUDY?**
You may choose to not allow your baby to take part in this study. You may take your baby out of this study at any time. Please talk to the study staff about other choices available to your baby. Whether or not you choose to allow your baby to take part in the study, the study staff will tell you about other sources of HIV-related care available to you and your baby.

**WHAT HAPPENS IF YOUR BABY IS INJURED?**
If your baby is injured as a result of being in this study, your baby will be given immediate treatment for the injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form. [Note to sites: This paragraph may be modified to reflect your institutional policies and procedures, but the statement regarding compensation through the NIH should not be changed.]

**WHAT ABOUT CONFIDENTIALITY?**

**US sites:**
Efforts will be made to keep your baby’s personal information confidential, but we cannot guarantee absolute confidentiality. Your baby’s personal information may be disclosed if required by law. Any publication of this study will not use your baby’s name or identify your baby personally.

To help us protect your baby’s privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify your baby, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify your baby, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the US Food and Drug Administration.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about your baby or your baby’s participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

Your baby’s study records may be reviewed by:

- [insert name of site IRB/EC]
- [insert name of site drug regulatory entity]
- [insert name of other site regulatory entities]
- The US National Institutes of Health and its study monitors
- The US Food and Drug Administration
• The US Office for Human Research Protections
• Other US, local, and international regulatory entities
• The IMPAACT Network that is coordinating the study
• The company that makes one of the ARVs given in this study (Merck Research Laboratories)

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify your baby. At most, the website will include a summary of the study results. You can search this website at any time.

Sites outside the US:
Efforts will be made to keep your baby’s personal information confidential, but we cannot guarantee absolute confidentiality. Your baby’s personal information may be disclosed if required by law. Any publication of this study will not use your baby’s name or identify your baby personally.

Your baby’s study records may be reviewed by:
• [insert name of site IRB/EC]
• [insert name of site drug regulatory entity]
• [insert name of other site regulatory entities]
• The US National Institutes of Health and its study monitors
• The US Food and Drug Administration
• The US Office for Human Research Protections
• Other US, local, and international regulatory entities
• The IMPAACT Network that is coordinating the study
• The company that makes one of the ARVs given in this study (Merck Research Laboratories)

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify your baby. At most, the website will include a summary of the study results. You can search this website at any time.

WHAT ARE THE COSTS TO ME?
There is no cost to you for your baby’s study visits, examinations, or blood tests. [Note to sites: This statement can be modified as needed for your site.]

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because your baby is taking part in a research study. [Note to sites: Language related to insurance can be deleted if it is not relevant to your site.]

WHAT ARE YOUR BABY’S RIGHTS AS A RESEARCH PARTICIPANT?
Taking part in this study is completely voluntary. You may choose to not allow your baby to take part in this study or take your baby out of the study at any time. Your decision will not have any impact on your baby’s participation in other studies conducted by the National Institutes of Health and will not result in any penalty or loss of benefits to which your baby is otherwise entitled.

We will tell you about new information from this or other studies that may affect your baby’s health and welfare, or your willingness for your baby to stay in this study. If you want to learn the results of this study when they are available, please let the study staff know.
WHAT SHOULD I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
  • name of the investigator or other study staff
  • telephone number of above

For questions about your baby’s rights as a research participant, contact:
  • name or title of person on the IRB/EC or other organization appropriate for the site
  • telephone number of above

SIGNATURES

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to allow your baby to take part in this study, please sign your name below.

Participant’s Name (print)

Parent or Legal Guardian Name (print)  Parent or Legal Guardian Signature  Date

Study Staff Conducting Consent Process Name (print)  Study Staff Signature  Date

Witness Name  Witness Signature  Date
BRIEF INFORMATION ABOUT STEPS 2, 3, AND 4

This sheet is for your information only and does not obtain informed consent for Steps 2, 3 and 4.

If you allow your baby to take part in Step 1 of this study, your baby will have study visits as described in the consent form for Step 1. If your baby is found to be infected with HIV, you will be asked to allow your baby to take part in Step 2. Step 2 will be explained to you in detail and you will be asked to sign a separate consent form for Step 2 at that time. Later, your baby may meet study requirements for Steps 3 and 4. If so, Steps 3 and 4 will be explained to you and you will be asked to sign separate consent forms for those steps.

Some information for you to know about Steps 2, 3, and 4 is as follows:

- In Step 2, babies will be given 4 anti-HIV medicines (ARVs). Blood tests will be done to check on babies’ health and the amount of HIV in their blood. As babies take ARVs, the amount of HIV in the blood is expected to drop to a level that cannot be detected by the study tests.

- Starting around 2 years of age, tests will be done to see if babies may qualify to enter Step 3. Babies who do not qualify for Step 3, will stay in Step 2 until 4 years of age.

- Babies who qualify for Step 3 will stop taking ARVs. They will be monitored closely, including checking for HIV in the blood. If HIV is found in the blood, babies will enter Step 4 and start taking ARVs again. Otherwise, they will stay in Step 3, not taking ARVs, for up to 5 years. Babies in Step 4 will stay in the study through 5 years of age or until 6 months after HIV is not detected in their blood, whichever is later.

In Steps 2, 3, and 4, babies will have study visits in which questions are asked about their health, medicines, and feeding. Babies will have physical examinations and blood drawn for study tests. At some times, babies will need to come to the clinic for frequent visits (for example, every week for 4-6 weeks). At other times, visits will be further apart (for example, every 4 weeks or every 12 weeks).

Please ask the study staff any questions you may have about this study. It is important that you have all of the information you need to decide whether to allow your baby to take part.
APPENDIX IV-B

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS
CLINICAL TRIALS GROUP (IMPAACT)

SAMPLE INFORMED CONSENT
INFANT: STEP 1 – REGIMEN 2RV

P1115: Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission:
        A Phase I/II Proof of Concept Study
Version 2.0, dated 17 September 2018

INTRODUCTION
You are being asked to allow your baby to take part in this research study because you have tested positive for the Human Immunodeficiency Virus (HIV), the virus that causes AIDS, and your baby may be infected with HIV. This study is sponsored by the United States National Institutes of Health. The doctor in charge of this study at this site is: (insert name of Investigator of Record). Before you decide if you want your baby to participate, we want you to know about the study.

This is a consent form. It gives information about the study. The study staff will talk with you about this information. You are free to ask questions at any time. If you allow your baby to take part in the study, you will be asked to sign this form. You will be offered a copy to keep.

WHY IS THIS STUDY BEING DONE?
The main purpose of this study is to find out if starting anti-HIV medicines (ARVs) within 48 hours of birth can make it possible for babies who are infected with HIV to control HIV so well that HIV cannot be detected in their blood. As of now, when children with HIV start taking ARVs, they usually need to keep taking them for life. For newborn babies who start ARVs very soon after birth, it might be possible to later stop taking ARVs for a prolonged period of time and still stay healthy. This has only been seen in one child so far. That child started ARVs soon after birth, then stopped ARVs and was able to stay healthy, with no HIV detected in the blood for more than 2 years. About 27 months after stopping ARVs, HIV was detected in the child’s blood, and the child restarted ARVs. The amount of HIV in the child’s blood quickly dropped, and the child has remained healthy. This study is being done to find out if this can be seen in other babies who start ARVs very soon after birth. This study is also looking at the levels of ARVs that are safe and work well for babies this young.

The study is also testing an experimental injection called VRC01. The study is looking at the safety of VRC01 when given to babies. It is also looking at the effect of VRC01 on the amount of HIV that can be detected in babies’ blood. For this study, VRC01 is given as in injection in the skin of the thigh.

VRC01 is an antibody against HIV. Antibodies are made by the immune system to fight infection. Antibodies can also be made in laboratories. VRC01 is made in a laboratory.

VRC01 has been tested in laboratory experiments and in animals and people. It has been tested in HIV-negative adults, HIV-positive adults, and babies born to HIV-positive mothers. Laboratory experiments have shown that VRC01 could help decrease the amount of HIV in the body. However, we are still in the early stages of testing VRC01 to find out what its effects may be.
WHAT DOES YOUR BABY HAVE TO DO AS PART OF THIS STUDY?
This study has four steps. At this time, you are being asked to allow your baby to take part only in Step 1. This step is for babies whose mothers have HIV and it is not yet known if the babies have HIV. The study will do testing to confirm if your baby has HIV.

- If your baby DOES NOT have HIV, he or she will be in Step 1 of the study for 12 weeks.
- If your baby DOES have HIV, you will be asked to allow your baby to take part in Step 2 of the study. Step 2 will be explained to you and you will be asked to sign another consent form for that step. An information sheet about Steps 2, 3, and 4 is attached to this form.

The rest of this form explains Step 1, which involves five visits. If you allow your baby to take part, the Entry Visit will continue today. The other visits will be in 1, 2, 4, and 12 weeks. The Entry Visit will take about 4 hours. The other visits will take 1-2 hours.

At the Entry Visit
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have about 2 teaspoons (10 mL) of blood drawn for:
  - Tests for HIV infection and the amount of HIV in the blood. For these tests, blood will be drawn two times, at least one hour apart, within the first 48 hours of birth.
  -Routine safety tests. These tests check for problems with your baby’s blood cells, liver, and kidneys, which can sometimes be side effects of ARVs.
  - Other HIV-related tests.
- Your baby will take ARVs. The ARVs may include raltegravir, nevirapine, and other ARVs chosen by the study doctor. The study staff will tell you about the ARVs and how to give them to your baby. Some ARVs will be given as part of the study. The study staff will explain where to obtain the other ARVs and whether your insurance will need to pay for them. [Note to sites: This paragraph may be modified to reflect usual ARV prescribing and dispensing practices at your site; please note, however that the ARVs provided in this step, other than raltegravir are not study-supplied and should be obtained from non-study sources.]
- Your baby will have an injection of VRC01. After the injection, your baby must stay in the clinic for at least 2 hours. During this time, study staff will check for reactions to the injection.

For 7 days after the injection of VRC01, you will be asked to take your baby’s temperature at home and write down how your baby is doing. We will show you how to do this. If your baby has any problems, you will be asked to contact the study staff and to bring your baby to the clinic. If your baby has any reactions to VRC01, such as redness where VRC01 was injected, we may take a photo of the reaction. The photo will help the doctors working on the study assess the reaction.

At the Week 1 and Week 2 Visits
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have less than 1 teaspoon (less than 5 mL) of blood drawn for safety tests and HIV-related tests. Tests of the amount of ARVs and VRC01 in the blood will also be done.

The results of your baby’s first tests for HIV infection will be known by the time of the Week 2 visit.

If your baby has HIV, Step 2 of the study will be explained to you and you will be asked to sign another consent form for that step. If you agree, your baby will enter Step 2.
If your baby does not have HIV, the ARVs started at the Entry Visit will be stopped and ARVs usually
given to prevent babies from getting HIV will be given instead. The study staff will explain this change to
you. Your baby will have two more visits (described below) and then will leave the study.

At the Week 4 Visit
• You will be asked about your baby’s health, medicines, and feeding.
• Your baby will have a physical examination.
• Your baby will have less than 1 teaspoon (less than 5 mL) of blood drawn only if the safety tests done
  at Week 2 showed abnormal results. Otherwise no blood will be collected.
• The study staff will refer you to other sources of care for your baby outside the study, including
  sources of ARVs and HIV testing. Even though your baby was not found to have HIV in this study,
  he or she could still test positive later. It is important that he or she be tested again at 6-10 weeks of
  age.

At the Week 12 Visit
• You will be asked about whether your baby had any HIV tests since the Week 4 visit.
• Your baby will have less than 1 teaspoon (less than 5 mL) of blood drawn for tests for HIV infection
  and other HIV-related tests
• The study staff will tell you how the get the results of your baby’s HIV test. As needed, they will also
  talk with you again other sources of care for your baby outside the study.

GENETIC TESTING
Some of the blood tests done for this study will look at how your baby’s genes (DNA) affect his or her
response to HIV and ARVs. The researchers will not contact you or your baby’s regular health care
provider with the results of these tests. This is because these tests are often done with experimental
procedures and the results should not be used to make decisions about your baby’s health care. However,
if the researchers decide that a result is important for your baby’s health care, the study doctor will be
notified. If you would like to be contacted with this sort of information, you must notify the study staff of
any changes of your address and phone number.

You may decide that you do not want your baby’s blood used for genetic testing. Your baby can still be in
this study even if you make this decision. Please read the following statement carefully and then mark
your initials in the appropriate space provided.

I allow my baby’s blood to be used for genetic testing as part of this study.

____________ Yes ______________ No ______________ Date

STORAGE OF BLOOD FOR FUTURE USE
After the tests planned to be done for this study are completed, some of your baby’s blood may be
leftover. The IMPAACT Network would like to keep this blood for other research in the future. If you
agree to this, your baby’s leftover blood samples will be stored and tested at special laboratory facilities
that may be in the US and other countries outside of [insert site country]. Only approved researchers will
have access to them. People who work at the facilities will also have access to your baby’s samples to
keep track of them. These people won’t have information that directly identifies your baby. Your baby’s
samples will not be sold or directly used to produce commercial products. All proposed research studies
using your baby’s samples will be reviewed by the IMPAACT Network. There is no time limit on how
long your baby’s samples will be stored.
The researchers will not contact you or your baby’s regular health care provider with the results of future research tests. This is because research tests are often done with experimental procedures and the results should not be used to make decisions about your baby’s health care. However, if the researchers decide that a result is important for your baby’s health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your baby’s leftover samples stored for future research. Your baby can still be in this study even if you make this decision. You may also withdraw consent for storage and future use of your baby’s samples at any time. If you withdraw your consent, the leftover samples will be destroyed.

Please read the following statements carefully and then mark your initials in the appropriate space provided.

I allow my baby’s leftover blood samples to be stored for use in future IMPAACT-approved, HIV-related research studies.

__________ Yes    __________ No    __________ Date

I allow my baby’s leftover blood samples to be used for genetic testing as part of future IMPAACT-approved, HIV-related research studies.

__________ Yes    __________ No    __________ Date

HOW MANY BABIES WILL BE IN THIS STUDY?
About 450 babies have already taken part in Step 1 of this study. Another 450, for a total of 900, are expected to take part.

HOW LONG WILL BABIES BE IN THIS STUDY?
Babies will be in Step 1 of the study for 12 weeks.

WHY WOULD THE DOCTOR TAKE YOUR BABY OFF THIS STUDY EARLY?
The study doctor may need to take your baby off Step 1 of this study early without your permission for the reasons listed below. If this happens, no further information will be collected, and no further study visits or laboratory tests will be done.

- You do not have HIV infection.
- Your baby stops coming to the clinic for study visits.
- The study doctor determines that further participation would be harmful to your baby’s health or well-being.
- The study is stopped or cancelled.

WHAT ARE THE RISKS OF THE STUDY?
Blood drawing may cause some discomfort, bleeding, or bruising where the needle enters the body. A small blood clot may form at the site where the blood was drawn or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur.
WHAT ARE THE RISKS OF ARVS?
Babies in Step 1 of this study will be given four ARVs. The ARVs will be started earlier than usual (before a baby is known to have HIV). Also, nevirapine will be given at a higher dose than usual. This dosing may have more side effects. For example, the ARVs could cause low blood cells.

Some of the possible side effects of raltegravir and nevirapine are listed below. These are the serious or common side effects that have a known or possible relationship with these ARVs. These are not complete lists of all side effects. The study staff will discuss these with you. They will also tell you about the side effects of other ARVs your baby will be given. Please ask the study staff any questions you may have about ARVs and their possible side effects. Please also contact the study staff with any concerns about your baby’s health and possible side effects.

**Raltegravir, (RAL, Isentress™)**
Merck Research Laboratories

The following side effects have been associated with raltegravir:

- Rash which can become severe or life-threatening. Contact the study staff right away if your baby develops a rash.
- Headache
- Nausea
- Stomach pain and diarrhea
- Tiredness
- Trouble sleeping
- Dizziness
- Depression, including suicidal thoughts and actions
- Feeling anxious, paranoia
- Changes in behavior, like low or high activity in children
- Clumsiness and lack of coordination
- Easy bleeding (decreased blood clotting, low platelet count)
- Muscle tenderness, weakness or injury which can be serious and lead to kidney damage

Hypersensitivity or “allergic” reactions may occur. These reactions can cause of some the symptoms listed above. They can also affect body organs such as the liver. If the liver is affected, this can be severe. Contact the study staff if your baby has signs of liver problems. These signs include:

- Yellowing of the skin or whites of the eyes
- Dark urine
- Pale stools
- Loss of appetite
- Nausea or vomiting
- Pain, aching, or tenderness on the right side below the ribs
- Tiredness or general feeling of illness

**Nevirapine (NVP)**
The following serious side effects have been associated with nevirapine:
Severe liver damage that can result in death may occur and is often associated with a rash. People with abnormal liver function tests before starting nevirapine and people with active Hepatitis B or C infection are at higher risk for liver damage. Contact the study staff if your baby has signs of liver problems. These signs are listed above.

Hypersensitivity or “allergic” reactions may occur. These reactions are rarely fatal. The symptoms that your baby may have are rash, fever, tiredness, muscle or joint aches, flu-like feeling, blisters, mouth sores, facial swelling, red eyes and irritation of the eyes, general feeling of discomfort, and/or liver damage described above, kidney problems, and/or changes in white blood cell levels.

Muscle break down causing muscle aches or pain has been observed in some people experiencing skin and/or liver reactions associated with nevirapine.

Rash is the most common side effect associated with nevirapine. Most rashes occur early during treatment. The rash may be severe and rarely may cause death.

The risk of developing any of the serious side effects listed above is greatest during the first few months of treatment, but these side effects also can occur later. If your baby develops any of the side effects listed above, no matter how long he or she has been receiving nevirapine, you must contact the study staff right away and before you give your baby the next dose. The study doctor will instruct you on what to do next. If you and your doctor then decide to stop your baby’s treatment because of liver damage, hypersensitivity or severe skin reactions, your baby should never take nevirapine again.

In addition to the serious side effects listed above, additional side effects include:

- Fever
- Headache
- Upset stomach (nausea, vomiting)

WHAT ARE THE RISKS OF VRC01?

VRC01 is experimental. It is not approved for use in adults or babies born to mothers with HIV. We do not know if VRC01 is safe to use in people. We also do not know if VRC01 is useful as a treatment for HIV. VRC01 is being tested in research studies to learn more about it. This study will help us learn about VRC01 in babies.

VRC01 will be given as an injection in the skin. This kind of injection can cause stinging, itchiness, discomfort, pain, soreness, redness, bruising, swelling, or a small cut where the needle enters the skin. Rarely, this kind of injection can cause infection.

As of March 2018, more than 3900 HIV-negative and HIV-positive adults have received VRC01 in research studies in the United States, Botswana, Malawi, South Africa, Zimbabwe, and other countries. Some people had mild or moderate reactions like itchiness, redness, or swelling where VRC01 was injected. Some people felt tired or had mild body discomfort, muscle or joint pain, headache, chills, or nausea after receiving injections. Some people had hives while VRC01 was being given or soon after VRC01 was given. In some cases, the hives were severe. One person had chest discomfort and one fainted. Some people had abnormal results on tests of their blood cells, liver, or kidneys. These came back to normal after a few days or weeks.

As of March 2018, 40 babies born to mothers who have HIV have received VRC01 in a research study being done by the IMPAACT network in the United States, South Africa, and Zimbabwe. Most of these babies had redness, swelling, or a small bruise where VRC01 was injected, which lasted for a short time.
No other effects thought to be caused by VRC01 have been seen, and no serious health problems have occurred.

It is possible that babies who receive VRC01 in this study could develop “resistance” to VRC01 or other antibodies like VRC01. If resistance develops, the antibodies may not be effective in helping to control the baby’s HIV. In this study, the risk of resistance is minimized by giving VRC01 with ARVs. Other antibodies that are different from VRC01 have been given to people for other illnesses. With those antibodies, most side effects happen within the first 24 hours including fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heartbeat or chest pain. Rarely, some antibodies have caused serious reactions that may be life-threatening.

One type of serious reaction may occur soon after getting an antibody. It includes difficulty breathing possibly leading to low blood oxygen, low blood pressure, hives or rash, and swelling in the mouth and face. A second type of serious reaction may occur several days to 3 weeks after getting an antibody. It includes hives or a rash, fever, big lymph nodes, muscle and joint pains, kidney problems, chest discomfort and shortness of breath. Rarely, antibodies used to treat other diseases have been linked to a blood disorder that interferes with blood clotting, cancer, damage to the heart muscle, and to the body’s immune system attacking healthy cells.

These rare side effects and reactions have not been seen in other studies of VRC01. However, it is possible that babies in this study could have these types of reactions. Babies could also have other side effects or reactions that we do not yet know about.

The study staff will closely check on babies in this study for side effects and reactions. Contact the study staff if any of these problems or any other problems occur.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
This study may be of no direct benefit to your baby. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DOES YOUR BABY HAVE BESIDES THIS STUDY?
You may choose to not allow your baby to take part in this study. You may take your baby out of this study at any time. Please talk to the study staff about other choices available to your baby. Whether or not you choose to allow your baby to take part in the study, the study staff will tell you about other sources of HIV-related care available to you and your baby.

WHAT HAPPENS IF YOUR BABY IS INJURED?
If your baby is injured as a result of being in this study, your baby will be given immediate treatment for the injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form. [Note to sites: This paragraph may be modified to reflect your institutional policies and procedures, but the statement regarding compensation through the NIH should not be changed.]

WHAT ABOUT CONFIDENTIALITY?
US sites:
Efforts will be made to keep your baby’s personal information confidential, but we cannot guarantee absolute confidentiality. Your baby’s personal information may be disclosed if required by law. Any publication of this study will not use your baby’s name or identify your baby personally.
To help us protect your baby’s privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify your baby, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify your baby, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the US Food and Drug Administration.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about your baby or your baby’s participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

Your baby’s study records may be reviewed by:
- [insert name of site IRB/EC]
- [insert name of site drug regulatory entity]
- [insert name of other site regulatory entities]
- The US National Institutes of Health and its study monitors
- The US Food and Drug Administration
- The US Office for Human Research Protections
- Other US, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The company that makes one of the ARVs given in this study (Merck Research Laboratories)

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify your baby. At most, the website will include a summary of the study results. You can search this website at any time.

Sites outside the US:
Efforts will be made to keep your baby’s personal information confidential, but we cannot guarantee absolute confidentiality. Your baby’s personal information may be disclosed if required by law. Any publication of this study will not use your baby’s name or identify your baby personally.

Your baby’s study records may be reviewed by:
- [insert name of site IRB/EC]
- [insert name of site drug regulatory entity]
- [insert name of other site regulatory entities]
- The US National Institutes of Health and its study monitors
- The US Food and Drug Administration
- The US Office for Human Research Protections
- Other US, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The company that makes one of the ARVs given in this study (Merck Research Laboratories)

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify your baby. At most, the website will include a summary of the study results. You can search this website at any time.
WHAT ARE THE COSTS TO ME?
There is no cost to you for your baby’s study visits, examinations, or blood tests. [Note to sites: This statement can be modified as needed for your site.]

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because your baby is taking part in a research study. [Note to sites: Language related to insurance can be deleted if it is not relevant to your site.]

WHAT ARE YOUR BABY’S RIGHTS AS A RESEARCH PARTICIPANT?
Taking part in this study is completely voluntary. You may choose to not allow your baby to take part in this study or take your baby out of the study at any time. Your decision will not have any impact on your baby’s participation in other studies conducted by the National Institutes of Health and will not result in any penalty or loss of benefits to which your baby is otherwise entitled.

We will tell you about new information from this or other studies that may affect your baby’s health and welfare, or your willingness for your baby to stay in this study. If you want to learn the results of this study when they are available, please let the study staff know.

WHAT SHOULD I DO IF I HAVE QUESTIONS OR PROBLEMS?
For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your baby’s rights as a research participant, contact:

- name or title of person on the IRB/EC or other organization appropriate for the site
- telephone number of above

SIGNATURES
If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to allow your baby to take part in this study, please sign your name below.

Participant’s Name (print)

Parent or Legal Guardian Name (print)       Parent or Legal Guardian Signature       Date

Study Staff Conducting Consent Process Name (print)       Study Staff Signature       Date

Witness Name       Witness Signature       Date
BRIEF INFORMATION ABOUT STEPS 2, 3, AND 4

This sheet is for your information only and does not obtain informed consent for Steps 2, 3 and 4.

If you allow your baby to take part in Step 1 of this study, your baby will have study visits as described in the consent form for Step 1. If your baby is found to be infected with HIV, you will be asked to allow your baby to take part in Step 2. Step 2 will be explained to you in detail and you will be asked to sign a separate consent form for Step 2 at that time. Later, your baby may meet study requirements for Steps 3 and 4. If so, Steps 3 and 4 will be explained to you and you will be asked to sign a separate consent forms for those steps.

Some information for you to know about Steps 2, 3, and 4 is as follows:

- In Step 2, babies will be given 4 anti-HIV medicines (ARVs). Babies will also be given 3 more injections of VRC01. Blood tests will be done to check on babies’ health and the amount of HIV in their blood. As babies take ARVs, the amount of HIV in the blood is expected to drop to a level that cannot be detected by the study tests.

- Starting around 2 years of age, tests will be done to see if babies may qualify to enter Step 3. Babies who do not qualify for Step 3, will stay in Step 2 until 4 years of age.

- Babies who qualify for Step 3 will stop taking ARVs. They will be monitored closely, including checking for HIV in the blood. If HIV is found in the blood, babies will enter Step 4 and start taking ARVs again. Otherwise, they will stay in Step 3, not taking ARVs, for up to 5 years. Babies in Step 4 will stay in the study through 5 years of age or until 6 months after HIV is not detected in their blood, whichever is later.

In Steps 2, 3, and 4, babies will have study visits in which questions are asked about their health, medicines, and feeding. Babies will have physical examinations and blood drawn for study tests. At some times, babies will need to come to the clinic for frequent visits (for example, every week for 4-6 weeks). At other times, visits will be further apart (for example, every 4 weeks or every 12 weeks).

Please ask the study staff any questions you may have about this study. It is important that you have all of the information you need to decide whether to allow your baby to take part.
APPENDIX IV-C

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS
CLINICAL TRIALS GROUP (IMPAACT)

SAMPLE INFORMED CONSENT
INFANT: STEP 2 – REGIMEN 1L AND 2R

P1115: Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission:
A Phase I/II Proof of Concept Study
Version 2.0, dated 17 September 2018

INTRODUCTION
You are being asked to allow your baby to take part in this research study because your baby has tested positive for HIV, the virus that causes AIDS, and started taking anti-HIV medicines (ARVs) within 48 hours after birth. This study is sponsored by the United States National Institutes of Health. The doctor in charge of this study at this site is: (insert name of Investigator of Record). Before you decide if you want your baby to participate, we want you to know about the study.

This is a consent form. It gives information about the study. The study staff will talk with you about this information. You are free to ask questions at any time. If you allow your baby to take part in the study, you will be asked to sign this form. You will be offered a copy to keep.

WHY IS THIS STUDY BEING DONE?
The main purpose of this study is to find out if starting ARVs within 48 hours of birth can make it possible for babies who are infected with HIV to control HIV so well that HIV cannot be detected in their blood. As of now, when children with HIV start taking ARVs, they usually need to keep taking them for life. For newborn babies who start ARVs very soon after birth, it might be possible to later stop taking ARVs for a prolonged period of time and still stay healthy. This has only been seen in one child so far. That child started ARVs soon after birth, then stopped ARVs and was able to stay healthy, with no HIV detected in the blood for more than 2 years. About 27 months after stopping ARVs, HIV was detected in the child’s blood, and the child restarted ARVs. The amount of HIV in the child’s blood quickly dropped, and the child has remained healthy. This study is being done to find out if this can be seen in other babies who start ARVs very soon after birth. This study is also looking at the levels of ARVs that are safe and work well for babies this young.

WHAT DOES YOUR BABY HAVE TO DO AS PART OF THIS STUDY?
This study has four steps. This form is for Step 2. If you allow your baby to take part, he or she will enter Step 2, and may later qualify for Step 3 or Step 4. We will discuss Steps 3 and 4 with you separately. At this time, you are only being asked to consider Step 2.

To take part in Step 2, testing must be done to confirm that your baby is infected with HIV. If the required test results are available from Step 1 of this study or your baby’s medical record, those results can be used for Step 2. If not, additional testing will be done for the study. About 1 teaspoon of blood (5 mL) will be drawn for this testing. If infection is not confirmed, your baby will no longer be able to take part in the study. The study staff will explain this to you and refer you to other sources of care for your baby outside the study. It is important that your baby be tested for HIV again at 6-10 weeks of age.
If you allow your baby to take part in Step 2, the Step 2 Entry Visit (described below) will continue today. After that, your baby may continue in Step 2 for about 4 years. Each visit in Step 2 will take about 2 hours.

**Step 2 Entry**
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have about 2 teaspoons (10 mL) of blood drawn for:
  - Routine safety tests. These tests check for problems with your baby’s blood cells, liver, and kidneys which can sometimes be side effects of ARVs.
  - Tests of how well the immune system is working and the amount of HIV in the blood.
  - Tests of the amount of ARVs in the blood.
  - Other HIV-related tests.
- Your baby will have about 1 teaspoon (5 mL) of urine collected for later testing. The later testing will look for an infection called cytomegalovirus.
- Your baby will continue taking ARVs. The ARVs may include raltegravir, lopinavir/ritonavir, nevirapine, and other ARVs chosen by the study doctor. The study staff will tell you about the ARVs and how to give them to your baby. Some ARVs will be given as part of the study. The study staff will explain where to obtain the other ARVs and whether your insurance will need to pay for them.
  
  [Note to sites: This paragraph may be modified to reflect usual ARV prescribing and dispensing practices at your site; please note, however that the ARVs provided in this step, other than raltegravir are not study-supplied and should be obtained from non-study sources.]

**Step 2 Visits in the First 6 Months**
*(Weeks 1, 2, 4, 5, 9, 12, 16, 20, and 24)*

There will be 9 visits in the first 6 months. The visits are close together at first (every 1-2 weeks) then further apart (every 4 weeks) as your baby gets older.
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have up to about 2 teaspoons (10 mL) of blood drawn for the same types of tests done at entry. Different safety and HIV-related tests will be done across visits. Tests of the amount of HIV in the blood will be done at most visits. Tests of the amount of ARVs in the blood will be done at some visits.
- During this time, your baby’s ARVs may be changed. For example, as your baby grows, doses may be increased. Some ARVs may be stopped and others may be started. As needed, you will be provided ARVs for your baby and instructions on how to give them to your baby. *[Note to sites: same as above.]*

**Step 2 Visits from 6 to 18 Months**
*(Weeks 28 to 72)*

Visits will occur every 4 weeks.
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination and blood draw (about 2-3 teaspoons or 10-15 mL) at every third visit (every 12 weeks). Different safety and HIV-related tests will be done across visits. Tests of the amount of HIV in the blood will be done every 12 weeks.
- At visits when physical examinations and blood draws are not done, it may be possible to complete the visits by phone.

IMPAACT P1115
FINAL Version 2.0
Page 130 of 169
17 September 2018
• During this time, your baby’s ARVs may be changed. Depending on the amount of HIV detected in the blood, one of the ARVs (nevirapine) may be stopped. Other changes may also be made. As needed, you will be provided ARVs for your baby and instructions on how to give them to your baby. [Note to sites: same as above.]

Step 2 Visits from 18 to 48 Months (4 Years) (Weeks 84 to 192)
Visits will occur every 12 weeks.
• You will be asked about your baby’s health, medicines, and feeding.
• Your baby will have a physical examination.
• Your baby will have about 2-4 teaspoons (10-20 mL) of blood drawn. Different safety and HIV-related tests will be done across visits. Tests of the amount of HIV in the blood will be done at each visit.
• During this time, your baby’s ARVs may be changed. As needed, you will be provided ARVs for your baby and instructions on how to give them to your baby. [Note to sites: same as above.]

During this time, your baby’s test results will be reviewed to see if your baby meets the study requirements to stop taking ARVs. If these requirements are met within 4 years, the study doctor will meet with you to discuss this. The doctor will tell you about your child’s health and latest test results. The doctor will also give you an update on what has been learned outside of this study about controlling HIV and starting and stopping ARVs. Because we expect to be learning new information over time, we want you to have the most up-to-date information. You are welcome to ask questions about this at any time.

If your child does not meet the requirements to stop taking ARVs, or you do not want your child to stop taking ARVs, your child will stay in the study for about 4 years. You child will then leave the study. The study staff will tell you about other sources of HIV-related care available to your baby at that time.

Other Procedures
[Sites may use locally appropriate terminology to refer to lumbar puncture]
A procedure called “lumbar puncture” is sometimes done when babies are sick. This procedure uses a needle to collect fluid from the baby’s spine. The fluid is then tested to find out what may be causing the baby to be sick. No lumbar punctures will be done for this study. However, if your baby has a lumbar puncture because of sickness not related to the study, we would like to keep any spinal fluid that may be left over for tests. The tests would look for HIV in the fluid. The tests may also look for other factors related to HIV and the immune system in the fluid.

You may decide that you do not want your baby’s leftover spinal fluid stored for tests. Your baby can still be in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my baby’s leftover spinal fluid blood to be stored for tests as part of this study (if my baby has a lumbar puncture outside the study).

____________________ Yes ________________ No ________________ Date
GENETIC TESTING
Some of the blood tests done for this study will look at how your baby’s genes (DNA) affect his or her response to HIV and ARVs. The researchers will not contact you or your baby’s regular health care provider with the results of these tests. This is because these tests are often done with experimental procedures and the results should not be used to make decisions about your baby’s health care. However, if the researchers decide that a result is important for your baby’s health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your child’s blood used for genetic testing. Your child can still be in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my child’s blood to be used for genetic testing as part of this study.

__________ Yes __________ No __________ Date

STORAGE OF BLOOD FOR FUTURE USE
After the tests planned to be done for this study are completed, some of your baby’s blood may be leftover. The IMPAACT Network would like to keep this blood for other research in the future. If you agree to this, your baby’s leftover blood samples will be stored and tested at special laboratory facilities that may be in the US and other countries outside of [insert site country]. Only approved researchers will have access to them. People who work at the facilities will also have access to your baby’s samples to keep track of them. These people won’t have information that directly identifies your baby. Your baby’s samples will not be sold or directly used to produce commercial products. All proposed research studies using your baby’s samples will be reviewed by the IMPAACT Network. There is no time limit on how long your baby’s samples will be stored.

The researchers will not contact you or your baby’s regular health care provider with the results of future research tests. This is because research tests are often done with experimental procedures and the results should not be used to make decisions about your baby’s health care. However, if the researchers decide that a result is important for your baby’s health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your baby’s leftover samples stored for future research. Your baby can still be in this study even if you make this decision. You may also withdraw consent for storage and future use of your baby’s samples at any time. If you withdraw your consent, the leftover samples will be destroyed.

Please read the following statements carefully and then mark your initials in the appropriate space provided.

I allow my baby’s leftover blood samples to be stored for use in future IMPAACT-approved, HIV-related research studies.

__________ Yes __________ No __________ Date
I allow my baby’s leftover blood samples to be used for genetic testing as part of future IMPAACT-approved, HIV-related research studies.

__________ Yes __________ No __________ Date

HOW MANY BABIES WILL BE IN THIS STUDY?
About 100 babies are expected to take part in Step 2 of this study.

HOW LONG WILL BABIES BE IN THIS STUDY?
Babies will be in Step 2 for up to 4 years.

When babies leave the study, they will no longer be able to get ARVs from the study. The study staff will tell you about other sources of HIV-related care and ARVs available to your baby. The ARVs given in the study may or may not be available from other sources. Because of this, your baby may need to start taking different ARVs when he or she leaves the study.

WHY WOULD THE DOCTOR TAKE YOUR BABY OFF THIS STUDY EARLY?
The study doctor may need to take your baby off the study early without your permission for the reasons listed below. If this happens, no further information will be collected, and no further study visits or laboratory tests will be done.

- Your baby does not have HIV infection.
- Your baby stops coming to the clinic for the study visits.
- The study doctor determines that further participation would be harmful to your baby’s health or well-being.
- Your baby does not qualify to top taking ARVs after 4 years in Step 2.
- The study is stopped or cancelled.

WHAT ARE THE RISKS OF THE STUDY?
Blood drawing may cause some discomfort, bleeding, or bruising where the needle enters the body. A small blood clot may form at the site where the blood was drawn or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur.

Babies in Step 2 will take ARVs. Usually three ARVs are given to HIV-infected babies. In this study, four ARVs will be given. Also, in the first two weeks, nevirapine will be given at a higher dose than usual. This dosing may have more side effects. For example, the ARVs could cause low blood cells.

Some of the possible side effects of raltegravir, lopinavir/ritonavir, and nevirapine are listed below. These are the serious or common side effects that have a known or possible relationship with these ARVs. These are not complete lists of all side effects. The study staff will discuss these with you. They will also tell you about the side effects of other ARVs your baby will be given. Please ask the study staff any questions you may have about ARVs and their possible side effects. Please also contact the study staff with any concerns about your baby’s health and possible side effects.

Raltegravir, (RAL, Isentress™)
Merck Research Laboratories

The following side effects have been associated with raltegravir:
• Rash which can become severe or life-threatening. Contact the study staff right away if your baby develops a rash.
• Headache
• Nausea
• Stomach pain and diarrhea
• Tiredness
• Trouble sleeping
• Dizziness
• Depression, including suicidal thoughts and actions
• Feeling anxious, paranoia
• Changes in behavior, like low or high activity in children
• Clumsiness and lack of coordination
• Easy bleeding (decreased blood clotting, low platelet count)
• Muscle tenderness, weakness or injury which can be serious and lead to kidney damage

Hypersensitivity or “allergic” reactions may occur. These reactions can cause some of the symptoms listed above. They can also affect body organs such as the liver. If the liver is affected, this can be severe. Contact the study staff if your baby has signs of liver problems. These signs include:

• Yellowing of the skin or whites of the eyes
• Dark urine
• Pale stools
• Loss of appetite
• Nausea or vomiting
• Pain, aching, or tenderness on the right side below the ribs
• Tiredness or general feeling of illness

Lopinavir/Ritonavir (LPV/r)
The following serious side effects are associated with lopinavir/ritonavir:

• Abnormal heart rhythm and electrocardiogram (EKG) changes. These changes can lead to serious heart problems. The risk for these problems may be higher if your baby:
  – Already has a history of abnormal heart rhythm or other types of heart disease
  – Take other medicines that can affect the heart rhythm while taking lopinavir/ritonavir
  If your baby develops abnormal heart rhythm he or she may experience lightheadedness, fainting spells or an abnormal heart beat.
• Pancreatitis (inflammation of the pancreas), which may cause death. If your baby develops pancreatitis, he or she may have one or more of the following: stomach pain, nausea, vomiting or abnormal pancreatic function blood tests.
• Increases in triglycerides and cholesterol in the blood.
• Liver problems and worsening liver disease, which may result in death. People with these conditions may have abnormal liver function blood tests. Contact the study staff if your baby has signs of liver problems. These signs are listed above.
• Rash, which could blister, and may be severe or life-threatening. Contact the study staff if your baby develops a rash.
Additional side effects may include:
- Abnormal bowel movements (stools), including loose or watery stools, upset stomach and stomach pain
- Feeling weak and tired
- Headache

Lopinavir/ritonavir is a type of ARV called a protease inhibitor. In addition to the side effects listed above, protease inhibitors may be associated with development of diabetes or worsening of high blood sugar. There have been reports of increased bleeding in HIV-infected persons with hemophilia who were treated with protease inhibitors. It is not known if the protease inhibitors were the cause of the increased bleeding.

**Nevirapine (NVP)**
The following serious side effects have been associated with nevirapine:

Severe liver damage that can result in death may occur and is often associated with a rash. People with abnormal liver function tests before starting nevirapine and people with active Hepatitis B or C infection are at higher risk for liver damage. Contact the study staff if your baby has signs of liver problems. These signs are listed above.

Hypersensitivity or “allergic” reactions may occur. These reactions are rarely fatal. The symptoms that your baby may have are rash, fever, tiredness, muscle or joint aches, flu-like feeling, blisters, mouth sores, facial swelling, red eyes and irritation of the eyes, general feeling of discomfort, and/or liver damage described above, kidney problems, and/or changes in white blood cell levels.

Muscle break down causing muscle aches or pain has been observed in some people experiencing skin and/or liver reactions associated with nevirapine.

Rash is the most common side effect associated with nevirapine. Most rashes occur early during treatment. The rash may be severe and rarely may cause death.

The risk of developing any of the serious side effects listed above is greatest during the first few months of treatment, but these side effects also can occur later. If your baby develops any of the side effects listed above, no matter how long he or she has been receiving nevirapine, you must contact the study staff right away and before you give your baby the next dose. The study doctor will instruct you on what to do next. If you and your doctor then decide to stop your baby’s treatment because of liver damage, hypersensitivity or severe skin reactions, your baby should never take nevirapine again.

In addition to the serious side effects listed above, additional side effects include:
- Fever
- Headache
- Upset stomach (nausea, vomiting)

**ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?**
This study may be of no direct benefit to your baby. Information learned from this study may help others who have HIV. This study may also help control the amount of HIV in your baby’s body.
WHAT OTHER CHOICES DOES YOUR BABY HAVE BESIDES THIS STUDY?
You may choose to not allow your baby to take part in this study. You may take your baby out of this study at any time. Please talk to the study staff about choices available to your baby. Whether or not you allow your baby to take part in the study, the study staff will tell you about other sources of HIV-related care available to you and your baby.

WHAT HAPPENS IF YOUR BABY IS INJURED?
If your baby is injured as a result of being in this study, your baby will be given immediate treatment for the injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form.

WHAT ABOUT CONFIDENTIALITY?
US sites:
Efforts will be made to keep your baby’s personal information confidential, but we cannot guarantee absolute confidentiality. Your baby’s personal information may be disclosed if required by law. Any publication of this study will not use your baby’s name or identify your baby personally.

To help us protect your baby’s privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify your baby, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify your baby, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the US Food and Drug Administration.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about your baby or your baby’s participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

Your baby’s study records may be reviewed by:
- [insert name of site IRB/EC]
- [insert name of site drug regulatory entity]
- [insert name of other site regulatory entities]
- The US National Institutes of Health and its study monitors
- The US Food and Drug Administration
- The US Office for Human Research Protections
- Other US, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The company that makes one of the ARVs given in this study (Merck Research Laboratories)

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify your baby. At most, the website will include a summary of the study results. You can search this website at any time.
Sites outside the US:
Efforts will be made to keep your baby’s personal information confidential, but we cannot guarantee absolute confidentiality. Your baby’s personal information may be disclosed if required by law. Any publication of this study will not use your baby’s name or identify your baby personally.

Your baby’s study records may be reviewed by:
- [insert name of site IRB/EC]
- [insert name of site drug regulatory entity]
- [insert name of other site regulatory entities]
- The US National Institutes of Health and its study monitors
- The US Food and Drug Administration
- The US Office for Human Research Protections
- Other US, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The company that makes one of the ARVs given in this study (Merck Research Laboratories)

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This web site will not include information that can identify your baby. At most, the web site will include a summary of the study results. You can search this web site at any time.

WHAT ARE THE COSTS TO ME?
There is no cost to you for your baby’s study visits, examinations, or blood tests.

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because your baby is taking part in a research study. [Note to sites: Language related to insurance can be deleted if it is not relevant to your site.]

WHAT ARE YOUR BABY’S RIGHTS AS A RESEARCH PARTICIPANT?
Taking part in this study is completely voluntary. You may choose not to allow your baby to take part in this study or take your baby out of the study at any time. Your decision will not have any impact on your baby’s participation in other studies conducted by the National Institutes of Health and will not result in any penalty or loss of benefits to which your baby is otherwise entitled.

If you choose to take your baby out of the study, the study staff will ask you to bring him or her back for a final visit. This visit will take about 1 hour and include answering questions about your baby’s health and medicines and a physical exam. About 1-2 teaspoons (5-10 mL) of blood will be drawn for HIV-related tests.

We will tell you about new information from this or other studies that may affect your baby’s health and welfare, or your willingness for your baby to stay in this study. If you want to learn the results of the study when they are available, please let the study staff know.
WHAT SHOULD I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
- name of the investigator or other study staff
- telephone number of above

For questions about your baby’s rights as a research participant, contact:
- name or title of person on the IRB/EC or other organization appropriate for the site
- telephone number of above

SIGNATURES

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to allow your baby to take part in this study, please sign your name below.

Participant’s Name (print)

<table>
<thead>
<tr>
<th>Parent or Legal Guardian Name (print)</th>
<th>Parent or Legal Guardian Name</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Signature</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Staff Conducting Consent Process Name (print)</th>
<th>Study Staff Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Witness Name</th>
<th>Witness Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
INTRODUCTION
You are being asked to allow your baby to take part in this research study because your baby has tested positive for HIV, the virus that causes AIDS, and started taking anti-HIV medicines (ARVs) within 48 hours after birth. This study is sponsored by the United States National Institutes of Health. The doctor in charge of this study at this site is: (insert name of Investigator of Record). Before you decide if you want your baby to participate, we want you to know about the study.

This is a consent form. It gives information about the study. The study staff will talk with you about this information. You are free to ask questions at any time. If you allow your baby to take part in the study, you will be asked to sign this form. You will be offered a copy to keep.

WHY IS THIS STUDY BEING DONE?
The main purpose of this study is to find out if starting ARVs within 48 hours of birth can make it possible for babies who are infected with HIV to control HIV so well that HIV cannot be detected in their blood. As of now, when children with HIV start taking ARVs, they usually need to keep taking them for life. For newborn babies who start ARVs very soon after birth, it might be possible to later stop taking ARVs for a prolonged period of time and still stay healthy. This has only been seen in one baby so far. That child started ARVs soon after birth, then stopped ARVs and was able to stay healthy, with no HIV detected in the blood for more than 2 years. About 27 months after stopping ARVs, HIV was detected in the child’s blood, and the child restarted ARVs. The amount of HIV in the child’s blood quickly dropped, and the child has remained healthy. This study is being done to find out if this can be seen in other babies who start ARVs very soon after birth. This study is also looking at the levels of ARVs that are safe and work well for babies this young.

The study is also testing an experimental injection called VRC01. The study is looking at the safety of VRC01 when given to babies. It is also looking at the effect of VRC01 on the amount of HIV that can be detected in babies’ blood. For this study, VRC01 is given as in injection in the skin of the thigh.

VRC01 is an antibody against HIV. Antibodies are made by the immune system to fight infection. Antibodies can also be made in laboratories. VRC01 is made in a laboratory.

VRC01 has been tested in laboratory experiments and in animals and people. It has been tested in HIV-negative adults, HIV-positive adults, and babies born to HIV-positive mothers. Laboratory experiments have shown that VRC01 could help decrease the amount of HIV in the body. However, we are still in the early stages of testing VRC01 to find out what its effects may be.
WHAT DOES YOUR BABY HAVE TO DO AS PART OF THIS STUDY?
This study has four steps. Your baby started the study in Step 1. This form is for Step 2. If you allow your baby to take part, he or she will enter Step 2, and may later qualify for Step 3 or Step 4. We will discuss Steps 3 and 4 with you separately. At this time, you are only being asked to consider Step 2.

If you allow your baby to take part in Step 2, the Step 2 Entry Visit (described below) will continue today. After that, your baby may continue in Step 2 for about 4 years. Most visits in Step 2 will take about 2 hours. Visits when VRC01 is given will take about 3-4 hours.

Step 2 Entry
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have about 2 teaspoons (10 mL) of blood drawn for:
  - Routine safety tests. These tests check for problems with your baby’s blood cells, liver, and kidneys which can sometimes be side effects of ARVs.
  - Tests of how well the immune system is working and the amount of HIV in the blood
  - Tests of the amount of ARVs in the blood.
  - Other HIV-related tests.
- Your baby will have about 1 teaspoon (5 mL) of urine collected for later testing. The later testing will look for an infection called cytomegalovirus.
- Your baby will continue taking ARVs. The ARVs may include raltegravir, lopinavir/ritonavir, nevirapine, and other ARVs chosen by the study doctor. The study staff will tell you about the ARVs and how to give them to your baby. Some ARVs will be given as part of the study. The study staff will explain where to obtain the other ARVs and whether your insurance will need to pay for them. [Note to sites: This paragraph may be modified to reflect usual ARV prescribing and dispensing practices at your site; please note, however that the ARVs provided in this step, other than raltegravir are not study-supplied and should be obtained from non-study sources.]
- Your baby will have an injection of VRC01. After the injection, your baby must stay in the clinic for at least 1 hour. During this time, study staff will check for reactions to the injection.

Step 2 Visits in the First 6 Months
(Weeks 1, 2, 4, 5, 8, 9, 12, 16, 20, and 24)
There will be 10 visits in the first 6 months. The visits are close together at first (every 1-2 weeks) then further apart (every 4 weeks) as your baby gets older.
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have up to about 2 teaspoons (10 mL) of blood drawn for the same types of tests done at entry. Different safety and HIV-related tests will be done across visits. Tests of the amount of HIV in the blood will be done at most visits. Tests of the amount of ARVs and VRC01 in the blood will be done at some visits.
- During this time, your baby’s ARVs may be changed. For example, as your baby grows, doses may be increased. Some ARVs may be stopped and others may be started. As needed, you will be provided ARVs for your baby and instructions on how to give them to your baby. [Note to sites: same as above.]
- At 4 and 8 weeks, your baby will have an injection of VRC01. After each injection, your baby must stay in the clinic for at least 1 hour. During this time, study staff will check for reactions to the injection.
For 7 days after each injection of VRC01, you will be asked to take your baby’s temperature at home and write down how your baby is doing. We will show you how to do this. After 3 days, we will telephone you to ask for the information you have written down. You can also come to the clinic with your baby or have a study staff member come to your home instead of having the telephone call. If your baby has any problems, you will be asked to tell the study staff and to bring your baby to the clinic. If your baby has any reactions to VRC01, such as redness where VRC01 was injected, we may take a photo of the reaction. The photo will help the doctors working on the study assess the reaction.

One injection of VRC01 was given to babies in Step 1. In Step 2, three more injections are planned to be given. However, injections may not be given to babies who are sick when injections are scheduled to be given. The study staff may stop giving injections to any baby if they determine that more injections might be harmful. Babies who miss any injections will still stay in the study.

**Step 2 Visits from 6 to 18 Months**
(Weeks 28 to 72)
Visits will occur every 4 weeks.
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination and blood draw (about 2-3 teaspoons or 10-15 mL) at every third visit (every 12 weeks). Different safety and HIV-related tests will be done across visits. Tests of the amount of HIV in the blood will be done every 12 weeks.
- At visits when physical examinations and blood draws are not done, it may be possible to complete the visits by phone.
- During this time, your baby’s ARVs may be changed. Depending on the amount of HIV detected in the blood, one of the ARVs (nevirapine) may be stopped. Other changes may also be made. As needed, you will be provided ARVs for your baby and instructions on how to give them to your baby. *(Note to sites: same as above.)*

**Step 2 Visits from 18 to 48 Months (4 Years)**
(Weeks 84 to 192)
Visits will occur every 12 weeks.
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have about 2-4 teaspoons (10-20 mL) of blood drawn. Different safety and HIV-related tests will be done across visits. Tests of the amount of HIV in the blood will be done at each visit.
- During this time, your baby’s ARVs may be changed. As needed, you will be provided ARVs for your baby and instructions on how to give them to your baby. *(Note to sites: same as above.)*

During this time, your baby’s test results will be reviewed to see if your baby meets the study requirements to stop taking ARVs. If these requirements are met within 4 years, the study doctor will meet with you to discuss this. The doctor will tell you about your child’s health and latest test results. The doctor will also give you an update on what has been learned outside of this study about controlling HIV and starting and stopping ARVs. Because we expect to be learning new information over time, we want you to have the most up-to-date information. You are welcome to ask questions about this at any time.

If your child does not meet the requirements to stop taking ARVs, or you do not want your child to stop taking ARVs, your child will stay in the study for about 4 years. You child will then leave the study. The study staff will tell you about other sources of HIV-related care available to your baby at that time.
Other Procedures

Sites may use locally appropriate terminology to refer to lumbar puncture

A procedure called “lumbar puncture” is sometimes done when babies are sick. This procedure uses a needle to collect fluid from the baby’s spine. The fluid is then tested to find out what may be causing the baby to be sick. No lumbar punctures will be done for this study. However, if your baby has a lumbar puncture because of sickness not related to the study, we would like to keep any spinal fluid that may be left over for tests. The tests would look for HIV in the fluid. The tests may also look for other factors related to HIV and the immune system in the fluid.

You may decide that you do not want your baby’s leftover spinal fluid stored for tests. Your baby can still be in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my baby’s leftover spinal fluid blood to be stored for tests as part of this study (if my baby has a lumbar puncture outside the study).

____________ Yes __________ No __________ Date

GENETIC TESTING

Some of the blood tests done for this study will look at how your baby’s genes (DNA) affect his or her response to HIV and ARVs. The researchers will not contact you or your baby’s regular health care provider with the results of these tests. This is because these tests are often done with experimental procedures and the results should not be used to make decisions about your baby’s health care. However, if the researchers decide that a result is important for your baby’s health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your child’s blood used for genetic testing. Your child can still be in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my child’s blood to be used for genetic testing as part of this study.

___________ Yes __________ No __________ Date

STORAGE OF BLOOD FOR FUTURE USE

After the tests planned to be done for this study are completed, some of your baby’s blood may be leftover. The IMPAACT Network would like to keep this blood for other research in the future. If you agree to this, your baby’s leftover blood samples will be stored and tested at special laboratory facilities that may be in the US and other countries outside of [insert site country]. Only approved researchers will have access to them. People who work at the facilities will also have access to your baby’s samples to keep track of them. These people won’t have information that directly identifies your baby. Your baby’s samples will not be sold or directly used to produce commercial products. All proposed research studies using your baby’s samples will be reviewed by the IMPAACT Network. There is no time limit on how long your baby’s samples will be stored.
The researchers will not contact you or your baby’s regular health care provider with the results of future research tests. This is because research tests are often done with experimental procedures and the results should not be used to make decisions about your baby’s health care. However, if the researchers decide that a result is important for your baby’s health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your baby’s leftover samples stored for future research. Your baby can still be in this study even if you make this decision. You may also withdraw consent for storage and future use of your baby’s samples at any time. If you withdraw your consent, the leftover samples will be destroyed.

Please read the following statements carefully and then mark your initials in the appropriate space provided.

I allow my baby’s leftover blood samples to be stored for use in future IMPAACT-approved, HIV-related research studies.

__________ Yes __________ No __________ Date

I allow my baby’s leftover blood samples to be used for genetic testing as part of future IMPAACT-approved, HIV-related research studies.

__________ Yes __________ No __________ Date

**HOW MANY BABIES WILL BE IN THIS STUDY?**
About 100 babies are expected to take part in Step 2 of this study.

**HOW LONG WILL BABIES BE IN THIS STUDY?**
Babies will be in Step 2 for up to 4 years.

When babies leave the study, they will no longer be able to get ARVs from the study. The study staff will tell you about other sources of HIV-related care and ARVs available to your baby. The ARVs given in the study may or may not be available from other sources. Because of this, your baby may need to start taking different ARVs when he or she leaves the study.

**WHY WOULD THE DOCTOR TAKE YOUR BABY OFF THIS STUDY EARLY?**
The study doctor may need to take your baby off the study early without your permission for the reasons listed below. If this happens, no further information will be collected, and no further study visits or laboratory tests will be done.

- Your baby does not have HIV infection.
- Your baby stops coming to the clinic for the study visits.
- The study doctor determines that further participation would be harmful to your baby’s health or well-being.
- Your baby does not qualify to top taking ARVs after 4 years in Step 2.
- The study is stopped or cancelled.
WHAT ARE THE RISKS OF THE STUDY?
Blood drawing may cause some discomfort, bleeding, or bruising where the needle enters the body. A small blood clot may form at the site where the blood was drawn or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur.

WHAT ARE THE RISKS OF ARVs?
Babies in Step 2 will take ARVs. Usually three ARVs are given to HIV-infected babies. In this study, four ARVs will be given. Also, in the first two weeks, nevirapin will be given at a higher dose than usual. This dosing may have more side effects. For example, the ARVs could cause low blood cells.

Some of the possible side effects of raltegravir, lopinavir/ritonavir, and nevirapine are listed below. These are the serious or common side effects that have a known or possible relationship with these ARVs. These are not complete lists of all side effects. The study staff will discuss these with you. They will also tell you about the side effects of other ARVs your baby will be given. Please ask the study staff any questions you may have about ARVs and their possible side effects. Please also contact the study staff with any concerns about your baby’s health and possible side effects.

Raltegravir, (RAL, Isentress™)
Merck Research Laboratories

The following side effects have been associated with raltegravir:

- Rash which can become severe or life-threatening. Contact the study staff right away if your baby develops a rash.
- Headache
- Nausea
- Stomach pain and diarrhea
- Tiredness
- Trouble sleeping
- Dizziness
- Depression, including suicidal thoughts and actions
- Feeling anxious, paranoia
- Changes in behavior, like low or high activity in children
- Clumsiness and lack of coordination
- Easy bleeding (decreased blood clotting, low platelet count)
- Muscle tenderness, weakness or injury which can be serious and lead to kidney damage

Hypersensitivity or “allergic” reactions may occur. These reactions can cause some of the symptoms listed above. They can also affect body organs such as the liver. If the liver is affected, this can be severe. Contact the study staff if your baby has signs of liver problems. These signs include:

- Yellowing of the skin or whites of the eyes
- Dark urine
- Pale stools
- Loss of appetite
- Nausea or vomiting
- Pain, aching, or tenderness on the right side below the ribs
- Tiredness or general feeling of illness
**Lopinavir/Ritonavir (LPV/r)**

The following serious side effects are associated with lopinavir/ritonavir:

- Abnormal heart rhythm and electrocardiogram (EKG) changes. These changes can lead to serious heart problems. The risk for these problems may be higher if your baby:
  - Already has a history of abnormal heart rhythm or other types of heart disease
  - Take other medicines that can affect the heart rhythm while taking lopinavir/ritonavir

  If your baby develops abnormal heart rhythm he or she may experience lightheadedness, fainting spells or an abnormal heart beat.

- Pancreatitis (inflammation of the pancreas), which may cause death. If your baby develops pancreatitis, he or she may have one or more of the following: stomach pain, nausea, vomiting or abnormal pancreatic function blood tests.

- Increases in triglycerides and cholesterol in the blood.

- Liver problems and worsening liver disease, which may result in death. People with these conditions may have abnormal liver function blood tests. Contact the study staff if your baby has signs of liver problems. These signs are listed above.

- Rash, which could blister, and may be severe or life-threatening. Contact the study staff if your baby develops a rash.

Additional side effects may include:

- Abnormal bowel movements (stools), including loose or watery stools, upset stomach and stomach pain
- Feeling weak and tired
- Headache

Lopinavir/ritonavir is a type of ARV called a protease inhibitor. In addition to the side effects listed above, protease inhibitors may be associated with development of diabetes or worsening of high blood sugar. There have been reports of increased bleeding in HIV-infected persons with hemophilia who were treated with protease inhibitors. It is not known if the protease inhibitors were the cause of the increased bleeding.

**Nevirapine (NVP)**

The following serious side effects have been associated with nevirapine:

Severe liver damage that can result in death may occur and is often associated with a rash. People with abnormal liver function tests before starting nevirapine and people with active Hepatitis B or C infection are at higher risk for liver damage. Contact the study staff if your baby has signs of liver problems. These signs are listed above.

Hypersensitivity reactions or “allergic” reactions may occur. These reactions are rarely fatal. The symptoms that your baby may have are rash, fever, tiredness, muscle or joint aches, flu-like feeling, blisters, mouth sores, facial swelling, red eyes and irritation of the eyes, general feeling of discomfort, and/or liver damage described above, kidney problems, and/or changes in white blood cell levels.

Muscle break down causing muscle aches or pain has been observed in some people experiencing skin and/or liver reactions associated with nevirapine.

Rash is the most common side effect associated with nevirapine. Most rashes occur early during treatment. The rash may be severe and rarely may cause death.
The risk of developing any of the serious side effects listed above is greatest during the first few months of treatment, but these side effects also can occur later. If your baby develops any of the side effects listed above, no matter how long he or she has been receiving nevirapine, you must contact the study staff right away and before you give your baby the next dose. The study doctor will instruct you on what to do next. If you and your doctor then decide to stop your baby’s treatment because of liver damage, hypersensitivity or severe skin reactions, your baby should never take nevirapine again.

In addition to the serious side effects listed above, additional side effects include:

- Fever
- Headache
- Upset stomach (nausea, vomiting)

**WHAT ARE THE RISKS OF VRC01?**

VRC01 is experimental. It is not approved for use in adults or babies born to mothers with HIV. We do not know if VRC01 is safe to use in people. We also do not know if VRC01 is useful as a treatment for HIV. VRC01 is being tested in research studies to learn more about it. This study will help us learn about VRC01 in babies.

VRC01 will be given as an injection in the skin. This kind of injection can cause stinging, itchiness, discomfort, pain, soreness, redness, bruising, swelling, or a small cut where the needle enters the skin. Rarely, this kind of injection can cause infection.

As of March 2018, more than 3900 HIV-negative and HIV-positive adults have received VRC01 in research studies in the United States, Botswana, Malawi, South Africa, Zimbabwe, and other countries. Some people had mild or moderate reactions like itchiness, redness, or swelling where VRC01 was injected. Some people felt tired or had mild body discomfort, muscle or joint pain, headache, chills, or nausea after receiving injections. Some people had hives while VRC01 was being given or soon after VRC01 was given. In some cases, the hives were severe. One person had chest discomfort and one fainted. Some people had abnormal results on tests of their blood cells, liver, or kidneys. These came back to normal after a few days or weeks.

As of March 2018, 40 babies born to mothers who have HIV have received VRC01 in a research study being done by the IMPAACT network in the United States, South Africa, and Zimbabwe. Most of these babies had redness, swelling, or a small bruise where VRC01 was injected, which lasted for a short time. No other effects thought to be caused by VRC01 have been seen, and no serious health problems have occurred.

It is possible that babies who receive VRC01 in this study could develop “resistance” to VRC01 or other antibodies like VRC01. If resistance develops, the antibodies may not be effective in helping to control the baby’s HIV. In this study, the risk of resistance is minimized by giving VRC01 with ARVs.

Other antibodies that are different from VRC01 have been given to people for other illnesses. With those antibodies, most side effects happen within the first 24 hours including fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heartbeat or chest pain. Rarely, some antibodies have caused serious reactions that may be life-threatening.
One type of serious reaction may occur soon after getting an antibody. It includes difficulty breathing possibly leading to low blood oxygen, low blood pressure, hives or rash, and swelling in the mouth and face. A second type of serious reaction may occur several days to 3 weeks after getting an antibody. It includes hives or a rash, fever, big lymph nodes, muscle and joint pains, kidney problems, chest discomfort and shortness of breath. Rarely, antibodies used to treat other diseases have been linked to a blood disorder that interferes with blood clotting, cancer, damage to the heart muscle, and to the body’s immune system attacking healthy cells.

These rare side effects and reactions have not been seen in other studies of VRC01. However, it is possible that babies in this study could have these types of reactions. Babies could also have other side effects or reactions that we do not yet know about.

The study staff will closely check on babies in this study for side effects and reactions. Contact the study staff if any of these problems or any other problems occur.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
This study may be of no direct benefit to your baby. Information learned from this study may help others who have HIV. This study may also help control the amount of HIV in your baby’s body.

WHAT OTHER CHOICES DOES YOUR BABY HAVE BESIDES THIS STUDY?
You may choose to not allow your baby to take part in this study. You may take your baby out of this study at any time. Please talk to the study staff about choices available to your baby. Whether or not you allow your baby to take part in the study, the study staff will tell you about other sources of HIV-related care available to you and your baby.

WHAT HAPPENS IF YOUR BABY IS INJURED?
If your baby is injured as a result of being in this study, your baby will be given immediate treatment for the injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form.

WHAT ABOUT CONFIDENTIALITY?

US sites:
Efforts will be made to keep your baby’s personal information confidential, but we cannot guarantee absolute confidentiality. Your baby’s personal information may be disclosed if required by law. Any publication of this study will not use your baby’s name or identify your baby personally.

To help us protect your baby’s privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify your baby, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify your baby, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the US Food and Drug Administration.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about your baby or your baby’s participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.
Your baby’s study records may be reviewed by:

- [insert name of site IRB/EC]
- [insert name of site drug regulatory entity]
- [insert name of other site regulatory entities]
- The US National Institutes of Health and its study monitors
- The US Food and Drug Administration
- The US Office for Human Research Protections
- Other US, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The company that makes one of the ARVs given in this study (Merck Research Laboratories)

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This web site will not include information that can identify your baby. At most, the web site will include a summary of the study results. You can search this web site at any time.

**Sites outside the US:**
Efforts will be made to keep your baby’s personal information confidential, but we cannot guarantee absolute confidentiality. Your baby’s personal information may be disclosed if required by law. Any publication of this study will not use your baby’s name or identify your baby personally.

Your baby’s study records may be reviewed by:

- [insert name of site IRB/EC]
- [insert name of site drug regulatory entity]
- [insert name of other site regulatory entities]
- The US National Institutes of Health and its study monitors
- The US Food and Drug Administration
- The US Office for Human Research Protections
- Other US, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The company that makes one of the ARVs given in this study (Merck Research Laboratories)

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This web site will not include information that can identify your baby. At most, the web site will include a summary of the study results. You can search this web site at any time.

**WHAT ARE THE COSTS TO ME?**
There is no cost to you for your baby’s study visits, examinations, or blood tests.

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because your baby is taking part in a research study. *[Note to sites: Language related to insurance can be deleted if it is not relevant to your site.]*

**WHAT ARE YOUR BABY’S RIGHTS AS A RESEARCH PARTICIPANT?**
Taking part in this study is completely voluntary. You may choose not to allow your baby to take part in this study or take your baby out of the study at any time. Your decision will not have any impact on your baby’s participation in other studies conducted by the National Institutes of Health and will not result in any penalty or loss of benefits to which your baby is otherwise entitled.
If you choose to take your baby out of the study, the study staff will ask you to bring him or her back for a final visit. This visit will take about 1 hour and include answering questions about your baby’s health and medicines and a physical exam. About 1-2 teaspoons (5-10 mL) of blood will be drawn for HIV-related tests.

We will tell you about new information from this or other studies that may affect your baby’s health and welfare, or your willingness for your baby to stay in this study. If you want to learn the results of the study when they are available, please let the study staff know.

WHAT SHOULD I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
- name of the investigator or other study staff
- telephone number of above

For questions about your baby’s rights as a research participant, contact:
- name or title of person on the IRB/EC or other organization appropriate for the site
- telephone number of above

SIGNATURES

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to allow your baby to take part in this study, please sign your name below.

____________________
Participant’s Name (print)

____________________  ______________________  __________
Parent or Legal Guardian Name (print)  Parent or Legal Guardian Signature  Date

____________________  ______________________  __________
Study Staff Conducting Consent Process Name (print)  Study Staff Signature  Date

____________________  ______________________  __________
Witness Name  Witness Signature  Date
INTRODUCTION
You are being asked if you want to have your child enter the part of this study in which children stop taking anti-HIV medicines (ARVs). Before you decide if you want your child to stop taking ARVs, we want you to know more about this part of the study.

This is a consent form. The study staff will talk with you about the information given in this form. The study doctor will also give you information on all that is known at this time about controlling HIV and starting and stopping ARVs. Because new information is learned over time, we want you to have the most up-to-date information. You are free to ask any questions. You can talk to other people about this or bring other people here to talk with the study staff before you decide. You can take as long as you need to decide. After all this discussion, you will record your decision at the end of this form. You will be offered a copy to keep.

This study is sponsored by the United States National Institutes of Health. The doctor in charge of this study at this site is: (insert name of Investigator of Record).

WHY IS THIS STUDY BEING DONE?
As you were told when your child first joined this study, the main purpose of this study is to find out if starting ARVs within 48 hours of birth can make it possible for babies who are infected with HIV to control HIV so well that HIV cannot be detected in their blood. As of now, when children with HIV start taking ARVs, they usually need to keep taking them for life. For newborn babies who start ARVs very soon after birth, it might be possible to later stop taking ARVs for a prolonged period of time and still stay healthy. This has only been seen in one child so far. That child started ARVs soon after birth, then stopped ARVs and was able to stay healthy, with no HIV detected in the blood for more than 2 years. About 27 months after stopping ARVs, HIV was detected in the child’s blood, and the child restarted ARVs. The amount of HIV in the child’s blood quickly dropped, and the child has remained healthy.

This study is being done to find out if this can be seen in other babies who start ARVs very soon after birth.

WHAT DOES YOUR CHILD HAVE TO DO AS PART OF THIS STUDY?
Your child has been taking part in Step 2 of this study. Based on tests done in Step 2, your child qualifies for Step 3. In Step 3, children stop taking ARVs. Children then have very frequent clinic visits to check on their health and see if HIV can be detected in their blood. There are some possible risks for children who stop taking ARVs. These are explained later in this form.

• If you decide that your child will enter Step 3, your child will stop taking ARVs and will have the study visits described in this form.
If you decide that your child will not enter Step 3, your child will keep taking ARVs and will stay in Step 2 until he or she is about 4 years old. We will keep you informed of your child’s health and test results. If you change your mind later, we will talk more with you about whether your child may qualify to stop taking ARVs at that time.

STEP 3 (Child Stops ARVs)
The clinic visits for Step 3 are described below. The first visit is the Step 3 Entry Visit. This visit may continue today or may be scheduled for another day.

Step 3 Entry Visit
- You will be asked about your child’s health and medicines.
- Your child will have a physical examination.
- Your child will have about 3-5 teaspoons (15-25 mL) of blood drawn for HIV-related tests.
- You will be instructed to stop giving ARVs to your child.

Step 3 Visits
After the Entry Visit, your child will have visits once each week for 4 weeks, then every 2 weeks, and then every 4 weeks. Each visit will take about 1-2 hours. At these visits:

- You will be asked about your child’s health and medicines.
- Your child will have a physical examination.
- Your child will have blood drawn for HIV-related tests. At different visits, the amount drawn will range from less than 1 teaspoon (less than 5 mL) to about 6 teaspoons (30 mL). Tests may also be done to detect ARVs.
- One of the tests done at each visit will check on whether HIV can be detected in your child’s blood. This test can be done with results available in a few hours. If you and your child are still in the clinic when the result is available, we will give you the result that day. Otherwise, we will contact you after the visit with the result. If the result shows that HIV is detected, you will be asked to return to the clinic with your child as soon as possible for the test to be repeated. The second test will be done as soon as possible and the result will be given to you when available.

After children stop taking ARVs, we expect that HIV will become detectable in their blood, but we do not know when this may happen. For some children, it may be within the first few weeks. For other children, it may be later.

For as long as HIV is not detected in your child’s blood, your child will remain in Step 3, not taking ARVs. If HIV is detected in your child’s blood on two tests, your child should start taking ARVs again. This is done in Step 4 of the study. Step 4 will be explained to you and you will be asked to sign another consent form for that step.

STEP 4 (Child Re-Starts ARVs)
The clinic visits for Step 4 are described below.

Step 4 Entry
- You will be asked about your child’s health and medicines.
- You will be instructed to start giving ARVs to your child again. As needed, you will be provided ARVs for your child and instructions on how to give them to your child. [Note to sites: This paragraph may be modified to reflect usual ARV prescribing and dispensing practices at your site.]
Your child will have a physical examination.
Your child will have about 2 teaspoons (10 mL) of blood drawn for safety tests and other HIV-related tests, including the amount of HIV in the blood.

Step 4 Visits
After the Entry Visit, your child will have visits every week, then every 2 weeks, then every 4 weeks, then every 12 weeks. At the first and third weeks, it may be possible to complete the visits by phone. Your child will keep having these visits until he or she reaches 5 years of age or until 6 months after HIV is not detected in your child’s blood, whichever is later. Each visit will take about 1-2 hours. At these visits:

- You will be asked about your child’s health, ARVs, and other medicines.
- As needed, you will be provided ARVs for your child and instructions on how to give them to your child. [Note to sites: same as above.]
- You child will have a physical examination.
- Your child will have blood drawn for safety tests and other HIV-related tests. At different visits, the amount drawn will range from less than 1 teaspoon (less than 5 mL) to about 4 teaspoons (20 mL).
- One of the tests done at each visit will check the amount of HIV in your child’s blood. This amount should go down as your child takes ARVs over time. We will check this closely and give you the test results. If the amount of HIV does not go down as expected, we will do tests for resistance. Resistance means than an ARV may not work well against the HIV in your child’s body. If tests show resistance, we will talk with you about other ARVs your child may be able to take.

Other Procedures
[Sites may use locally appropriate terminology to refer to lumbar puncture]
A procedure called “lumbar puncture” is sometimes done when children are sick. This procedure uses a needle to collect fluid from the child’s spine. The fluid is then tested to find out what may be causing the child to be sick. No lumbar punctures will be done for this study. However, if your child has a lumbar puncture because of sickness not related to the study, we would like to keep any spinal fluid that may be left over for tests. The tests would look for HIV in the fluid. The tests may also look for other factors related to HIV and the immune system in the fluid.

You may decide that you do not want your child’s leftover spinal fluid stored for tests. Your child can still be in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my child’s leftover spinal fluid blood to be stored for tests as part of this study (if my child has a lumbar puncture outside the study).

_____________ Yes   ____________ No   ____________ Date

GENETIC TESTING
Some of the blood tests done for this study will look at how your child’s genes (DNA) affect his or her response to HIV and ARVs. The researchers will not contact you or your child’s regular health care provider with the results of these tests. This is because these tests are often done with experimental procedures and the results should not be used to make decisions about your child’s health care. However, if the researchers decide that a result is important for your child’s health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.
You may decide that you do not want your child’s blood used for genetic testing. Your child can still be in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my child’s blood to be used for genetic testing as part of this study.

__________ Yes  ___________ No  ___________ Date

STORAGE OF BLOOD FOR FUTURE USE
After the tests planned to be done for this study are completed, some of your child’s blood may be leftover. The IMPAACT Network would like to keep this blood for other research in the future. If you agree to this, your child’s leftover samples will be stored and tested at special laboratory facilities that may be in the US and other countries outside of [insert site country]. Only approved researchers will have access to them. People who work at the facilities will also have access to your child’s samples to keep track of them. These people won’t have information that directly identifies your child. Your child’s samples will not be sold or directly used to produce commercial products. All proposed research studies using your child’s samples will be reviewed by the IMPAACT Network. There is no time limit on how long your child’s samples will be stored.

The researchers will not contact you or your child’s regular health care provider with the results of future research tests. This is because research tests are often done with experimental procedures and the results should not be used to make decisions about your child’s health care. However, if the researchers decide that a result is important for your child’s health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your child’s leftover samples stored for future research. Your child can still be in this study even if you make this decision. You may also withdraw consent for storage and future use of your child’s samples at any time. If you withdraw your consent, the leftover samples will be destroyed.

Please read the following statements carefully and then mark your initials in the appropriate space provided.

I allow my child’s leftover blood samples to be stored for use in future IMPAACT-approved, HIV-related research studies.

__________ Yes  ___________ No  ___________ Date

I allow my child’s leftover blood samples to be used for genetic testing as part of future IMPAACT-approved, HIV-related research studies.

__________ Yes  ___________ No  ___________ Date

HOW MANY CHILDREN WILL BE IN THIS STUDY?
About 100 children with HIV are expected to take part in this study. At this time, we do not know how many children will enter Step 3 or Step 4.

HOW LONG WILL CHILDREN BE IN THIS STUDY?
Children will stay in Step 3 for as long as HIV is not detected in their blood, up to 5 years.
Children who enter Step 4 will stay in Step 4 they reach 5 years of age or until 6 months after HIV is not detected in their blood. Then they will leave the study.

WHY WOULD THE DOCTOR TAKE YOUR CHILD OFF THIS STUDY EARLY?
The study doctor may need to take your child off the study early without your permission for the reasons listed below. If this happens, no further information will be collected, and no further study visits or laboratory tests will be done.

- Your child stops coming to the clinic for study visits.
- The study doctor determines that further participation would be harmful to your child’s health or well-being.
- The study is stopped or cancelled.

WHAT ARE THE RISKS OF THE STUDY?
Blood drawing may cause some discomfort, bleeding, or bruising where the needle enters the body. A small blood clot may form at the site where the blood was drawn or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur.

For children who stop taking ARVs, the amount of HIV in the blood may rise to detectable levels. This could also lead to HIV becoming resistant to ARVs. To avoid this, tests will be done frequently to check for HIV in the blood, and ARVs will be started again if HIV becomes detectable. It is important for your child to come for clinic visits as scheduled for these tests.

For children who start taking ARVs again, ARVs can cause side effects. The study staff have discussed side effects with you while your child has been in Step 2 of the study. They will tell you about the possible side effects of the ARVs your child will be taking in Step 4. Please ask any questions you may have. Please also contact the study staff with any concerns about your child’s health and possible side effects.

There may be other risks that are not yet known.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
This study may be of no direct benefit to your child. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DOES YOUR CHILD HAVE BESIDES THIS STUDY?
You may decide that you do not want your child to stop taking ARVs. In that case, your child can stay in the study (in Step 2) until he or she is about 4 years of age. If you decide that your child will stop taking ARVs now, you can change your mind later. In that case, your child can stay in the study (in Step 4). You may also take your child out of this study at any time. Please talk to the study staff about the choices available to your child. No matter what you decide, the study staff will tell you about other sources of HIV-related care available to you and your child.

WHAT HAPPENS IF YOUR CHILD IS INJURED?
If your child is injured as a result of being in this study, your child will be given immediate treatment for the injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form.
WHAT ABOUT CONFIDENTIALITY?
US sites:
Efforts will be made to keep your child’s personal information confidential, but we cannot guarantee absolute confidentiality. Your child’s personal information may be disclosed if required by law. Any publication of this study will not use your child’s name or identify your child personally.

To help us protect your child’s privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify your child, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify your child, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the US Food and Drug Administration.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about your child or your child’s participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

Your child’s study records may be reviewed by:
• [insert name of site IRB/EC]
• [insert name of site drug regulatory entity]
• [insert name of other site regulatory entities]
• The US National Institutes of Health and its study monitors
• The US Food and Drug Administration
• The US Office for Human Research Protections
• Other US, local, and international regulatory entities
• The IMPAACT Network that is coordinating the study
• The company that makes one of the ARVs given in this study (Merck Research Laboratories)

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This web site will not include information that can identify your child. At most, the web site will include a summary of the study results. You can search this web site at any time.

Sites outside the US:
Efforts will be made to keep your child’s personal information confidential, but we cannot guarantee absolute confidentiality. Your child’s personal information may be disclosed if required by law. Any publication of this study will not use your child’s name or identify your child personally.

Your child’s study records may be reviewed by:
• [insert name of site IRB/EC]
• [insert name of site drug regulatory entity]
• [insert name of other site regulatory entities]
• The US National Institutes of Health and its study monitors
• The US Food and Drug Administration
• The US Office for Human Research Protections
• Other US, local, and international regulatory entities
• The IMPAACT Network that is coordinating the study
• The company that makes one of the ARVs given in this study (Merck Research Laboratories)

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This web site will not include information that can identify your child. At most, the web site will include a summary of the study results. You can search this web site at any time.

WHAT ARE THE COSTS TO ME?
There is no cost to you for your child’s study visits, examinations, or blood tests.

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because your child is taking part in a research study. [Note to sites: Language related to insurance can be deleted if it is not relevant to your site.]

WHAT ARE YOUR CHILD’S RIGHTS AS A RESEARCH PARTICIPANT?
Taking part in this study is completely voluntary. You may choose not to allow your child to take part in this study or take your child out of the study at any time. Your decision will not have any impact on your child’s participation in other studies conducted by the National Institutes of Health and will not result in any penalty or loss of benefits to which your child is otherwise entitled.

If you choose to take your child out of the study, the study staff will ask you to bring him or her back for a final visit. This visit will take about 1 hour and include answering questions about your child’s health and medicines and a physical exam. About 1-2 teaspoons (5-10 mL) of blood will be drawn for HIV-related tests.

We will tell you about new information from this or other studies that may affect your child’s health and welfare, or your willingness for your child to stay in this study. If you want to learn the results of the study when they are available, please let the study staff know.

WHAT SHOULD I DO IF I HAVE QUESTIONS OR PROBLEMS?
For questions about this study or a research-related injury, contact:
• name of the investigator or other study staff
• telephone number of above

For questions about your child’s rights as a research participant, contact:
• name or title of person on the IRB/EC or other organization appropriate for the site
• telephone number of above
SIGNATURES

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to allow your child to take part in Steps 3 and 4 of this study, please sign your name below.

<table>
<thead>
<tr>
<th>Participant’s Name (print)</th>
<th>Parent or Legal Guardian Name (print)</th>
<th>Parent or Legal Guardian Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Staff Conducting Consent Process Name (print)</th>
<th>Study Staff Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Witness Name</th>
<th>Witness Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX IV-F
DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS
CLINICAL TRIALS GROUP (IMPAACT)

SAMPLE INFORMED CONSENT
MOTHER: COHORT 1

P1115: Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission:
A Phase I/II Proof of Concept Study
Version 2.0, dated 17 September 2018

INTRODUCTION
You are being asked to take part in this research study because you have tested positive for the Human Immunodeficiency Virus (HIV), the virus that causes AIDS, and your baby may also be infected with HIV. This study is sponsored by the United States National Institutes of Health. The doctor in charge of this study at this site is: (insert name of Investigator of Record). Before you decide if you want to participate, we want you to know about the study.

This is a consent form. It gives information about the study. The study staff will talk with you about this information. You are free to ask questions at any time.

WHY IS THIS STUDY BEING DONE?
The main purpose of this study is to find out if starting anti-HIV medicines (ARVs) within 48 hours of birth can make it possible for babies who are infected with HIV to control HIV so well that HIV cannot be detected in their blood. As of now, when children with HIV start taking ARVs, they usually need to keep taking them for life. For newborn babies who start ARVs very soon after birth, it might be possible to later stop taking ARVs for a prolonged period of time and still stay healthy. This has only been seen in one child so far. That child started ARVs soon after birth, then stopped ARVs and was able to stay healthy, with no HIV detected in the blood for more than 2 years. About 27 months after stopping ARVs, HIV was detected in the child’s blood, and the child restarted ARVs. The amount of HIV in the child’s blood quickly dropped, and the child has remained healthy. This study is being done to find out if this can be seen in other babies who start ARVs very soon after birth. This study is also looking at the levels of ARVs that are safe and work well for babies this young.

Although this study is focusing on babies, mothers’ participation is also important. This form gives information about study participation for mothers. You will also be given information about study participation for babies. If you choose to take part in the study with your baby, you will be asked to sign this form and a separate form for your baby. You will be offered copies of the forms to keep.

WHAT DO I HAVE TO DO AS PART OF THIS STUDY?
You must agree to take part in this study in order for your baby to take part. The amount of time you will be in this study and the number of visits you will have depends on whether your baby is found to be infected with HIV.

- If your baby DOES NOT have HIV, you will have one study visit, the Entry Visit described below.
- If your baby DOES have HIV, you will have two visits, the Entry Visit described below and another visit when your baby is found to have HIV. You will then have visits every 6 months for as long as your baby is in the study.
If you agree to take part in the study, the Entry Visit will continue today. This visit and all other visits are described below. Each visit will take 1-2 hours.

**At the Entry Visit**
- You will be asked questions about your health and medicines, including ARVs.
- Your medical record will be reviewed and information about your HIV infection and how well your immune system is working will be collected.
- Depending on the information available in your medical record, it may be necessary to do additional HIV tests for the study. A test of the amount of HIV in your blood will also be done. Up to 2 teaspoons of blood (10 mL) will be drawn for this testing. The results of these tests will be given to you.
- You will have about 2 teaspoons of blood (10 mL) drawn and stored for HIV-related testing to be done in the future.

**At the Visit When Your Baby is Found to Have HIV**
The results of your and your baby’s first tests for HIV infection will be known within 2 weeks after you enter the study. If you and/or your baby are not infected with HIV, you will have no further study visits for yourself, but you are asked to return with your baby for his or her visits.

If you and your baby are infected with HIV:
- You will be asked questions about your health and medicines, including ARVs.
- Your medical record will be reviewed and information about your HIV infection and how well your immune system is working will be collected.
- You will have about 3 teaspoons of blood (15 mL) drawn and stored for HIV-related testing to be done in the future.

**At Visits Every 6 Months**
- You will be asked questions about your health and medicines, including ARVs.
- Your medical record will be reviewed and information about your HIV infection and how well your immune system is working will be collected.

**GENETIC TESTING**
Some of the blood tests done for this study will look at how your genes (DNA) may affect your baby’s response to HIV and ARVs. The researchers will not contact you or your regular health care provider with the results of these tests. This is because these tests are often done with experimental procedures and these results should not be used to make decisions about your health care. However, if the researchers decide that a result is important for your health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your blood used for genetic testing. You can still be in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my blood to be used for genetic testing as part of this study.

____________ Yes   ____________ No   ____________ Date
STORAGE OF BLOOD FOR FUTURE USE

After the tests planned to be done for this study are completed, some of your blood may be leftover. The IMPAACT Network would like to keep this blood for other research in the future. If you agree to this, your leftover blood samples will be stored and tested at special laboratory facilities that may be in the US and other countries outside of [insert site country]. Only approved researchers will have access to them. People who work at the facilities will also have access to your samples to keep track of them. These people won’t have information that directly identifies you. Your samples will not be sold or directly used to produce commercial products. All proposed research studies using your samples will be reviewed by the IMPAACT Network. There is no time limit on how long your samples will be stored.

The researchers will not contact you or your regular health care provider with the results of future research tests. This is because research tests are often done with experimental procedures and the results should not be used to make decisions about your health care. However, if the researchers decide that a result is important for your health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your leftover samples stored for future research. You can still be in this study even if you make this decision. You may also withdraw your consent for storage and future use of your samples at any time. If you withdraw your consent, the leftover samples will be destroyed.

Please read the following statements carefully and then mark your initials in the appropriate space provided.

I allow my leftover blood samples to be stored for use in future IMPAACT-approved, HIV-related research studies.

____________ Yes  __________ No  __________ Date

I allow my leftover blood to be used for genetic testing as part of future IMPAACT-approved, HIV-related research studies.

____________ Yes  __________ No  __________ Date

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
About 450 mothers and babies have already taken part in this study. Another 450, for a total of about 900, are expected to take part.

HOW LONG WILL I BE IN THIS STUDY?
The amount of time you will be in this study depends on whether your baby is infected with HIV. If your baby is not infected with HIV, you will have one study visit. If your baby is infected with HIV, you will be in the study for as long as your baby, up to 9 years.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?
The study doctor may need to take you off the study early without your permission for the reasons listed below. If this happens, no further information will be collected, and no further study visits or laboratory tests will be done.

- You and/or your baby do not have HIV infection.
- Your baby meets conditions to leave the study.
- You stop coming to the clinic for study visits.
• The study doctor determines that further participation would be harmful to your health or well-being.
• The study is stopped or cancelled.

WHAT ARE THE RISKS OF THE STUDY?
Blood drawing may cause some discomfort, bleeding, or bruising where the needle enters the body. A small blood clot may form at the site where the blood was drawn or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
This study may be of no direct benefit to you or your baby. Information learned from this study may help others who have HIV. If your baby is infected with HIV, this study may help control the amount of HIV in your baby’s body.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?
You may choose to not take part in this study. You may leave the study at any time. Please talk to the study staff about other choices available to you. This study does not provide HIV-related care and treatment for mothers. Whether or not you choose to take part in the study, the study staff will tell you about other sources of HIV-related care available to you and your baby.

WHAT HAPPENS IF I AM INJURED?
If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form. [Note to sites: This paragraph may be modified to reflect your institutional policies and procedures, but the statement regarding compensation through the NIH should not be changed.]

WHAT ABOUT CONFIDENTIALITY?
US sites
Efforts will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the US Food and Drug Administration.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.
Your study records may be reviewed by:
• [insert name of site IRB/EC]
• [insert name of site drug regulatory entity]
• [insert name of other site regulatory entities]
• The US National Institutes of Health and its study monitors
• The US Food and Drug Administration
• The US Office for Human Research Protections
• Other US, local, and international regulatory entities
• The IMPAACT Network that is coordinating the study
• The company that makes one of the ARVs given to babies in this study (Merck Research Laboratories)

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the study results. You can search this website at any time.

Sites outside the US:
Efforts will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your study records may be reviewed by:
• [insert name of site IRB/EC]
• [insert name of site drug regulatory entity]
• [insert name of other site regulatory entities]
• The US National Institutes of Health and its study monitors
• The US Food and Drug Administration
• The US Office for Human Research Protections
• Other US, local, and international regulatory entities
• The IMPAACT Network that is coordinating the study
• The company that makes one of the ARVs given to babies in this study (Merck Research Laboratories)

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the study results. You can search this website at any time.

WHAT ARE THE COSTS TO ME?
There is no cost to you for your study visits or blood tests.

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study. [Note to sites: Language related to insurance can be deleted if it is not relevant to your site.]
WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?
Taking part in this study is completely voluntary. You may choose to not take part in this study. However, if you choose to not take part, your baby cannot take part. If you choose to take part, you may leave this study at any time. If you leave the study, your baby can stay in the study, if you agree to that. Your decisions will not have any impact on your participation in other studies conducted by the National Institutes of Health and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want to learn the results of this study when they are available, please let the study staff know.

WHAT SHOULD I DO IF I HAVE QUESTIONS OR PROBLEMS?
For questions about this study or a research-related injury, contact:
- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research participant, contact:
- name or title of person on the IRB/EC or other organization appropriate for the site
- telephone number of above

SIGNATURES
If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to take part in this study, please sign your name below.

Participant’s Name (print)  Participant Signature  Date

Study Staff Conducting Consent Process Name (print)  Study Staff Signature  Date

Witness Name  Witness Signature  Date
APPENDIX IV-G

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS
CLINICAL TRIALS GROUP (IMPAACT)

SAMPLE INFORMED CONSENT
MOTHER: COHORT 2

P1115: Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission:
A Phase I/II Proof of Concept Study
Version 2.0, dated 17 September 2018

INTRODUCTION
You are being asked to take part in this research study because you and your baby have tested positive for
the Human Immunodeficiency Virus (HIV), the virus that causes AIDS. This study is sponsored by the
United States National Institutes of Health. The doctor in charge of this study at this site is: (insert name
of Investigator of Record). Before you decide if you want to participate, we want you to know about the
study.

This is a consent form. It gives information about the study. The study staff will talk with you about this
information. You are free to ask questions at any time.

WHY IS THIS STUDY BEING DONE?
The main purpose of this study is to find out if starting anti-HIV medicines (ARVs) within 48 hours of
birth can make it possible for babies who are infected with HIV to control HIV so well that HIV cannot
be detected in their blood. As of now, when children with HIV start taking ARVs, they usually need to
keep taking them for life. For newborn babies who start ARVs very soon after birth, it might be possible
to later stop taking ARVs for a prolonged period of time and still stay healthy. This has only been seen in
one child so far. That child started ARVs soon after birth, then stopped ARVs and was able to stay
healthy, with no HIV detected in the blood for more than 2 years. About 27 months after stopping ARVs,
HIV was detected in the child’s blood, and the child restarted ARVs. The amount of HIV in the child’s
blood quickly dropped, and the child has remained healthy. This study is being done to find out if this can
be seen in other babies who start ARVs very soon after birth. This study is also looking at the levels of
ARVs that are safe and work well for babies this young.

Although this study is focusing on babies, mothers’ participation is also important. This form gives
information about study participation for mothers. You will also be given information about study
participation for babies. If you choose to take part in the study with your baby, you will be asked to sign
this form and a separate form for your baby. You will be offered copies of the forms to keep.

WHAT DO I HAVE TO DO AS PART OF THIS STUDY?
You must agree to take part in this study in order for your baby to take part. The amount of time you will
be in this study and the number of visits you will have depends on how long your baby stays in the study.

If you agree to take part in the study, the Entry Visit will continue today. This visit and all other visits are
described below. Each visit will take 1-2 hours.
At the Entry Visit

- You will be asked questions about your health and medicines, including ARVs.
- Your medical record will be reviewed and information about your HIV infection and how well your immune system is working will be collected.
- Depending on the information available in your medical record, it may be necessary to do additional HIV tests for the study. A test of the amount of HIV in your blood will also be done. Up to 2 teaspoons of blood (10 mL) will be drawn for this testing. The results of these tests will be given to you.
- You will have about 5 teaspoons of blood (25 mL) drawn and stored for HIV-related testing to be done in the future.

At Visits Every 6 Months

- You will be asked questions about your health and medicines, including ARVs.
- Your medical record will be reviewed and information about your HIV infection and how well your immune system is working will be collected.

GENETIC TESTING

Some of the blood tests done for this study will look at how your genes (DNA) may affect your baby’s response to HIV and ARVs. The researchers will not contact you or your regular health care provider with the results of these tests. This is because these tests are often done with experimental procedures and these results should not be used to make decisions about your health care. However, if the researchers decide that a result is important for your health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your blood used for genetic testing. You can still be in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my blood to be used for genetic testing as part of this study.

____________ Yes  ___________ No  ___________ Date

STORAGE OF BLOOD FOR FUTURE USE

After the tests planned to be done for this study are completed, some of your blood may be leftover. The IMPAACT Network would like to keep this blood for other research in the future. If you agree to this, your leftover blood samples will be stored and tested at special laboratory facilities that may be in the US and other countries outside of [insert site country]. Only approved researchers will have access to them. People who work at the facilities will also have access to your samples to keep track of them. These people won’t have information that directly identifies you. Your samples will not be sold or directly used to produce commercial products. All proposed research studies using your samples will be reviewed by the IMPAACT Network. There is no time limit on how long your samples will be stored.

The researchers will not contact you or your regular health care provider with the results of future research tests. This is because research tests are often done with experimental procedures and the results should not be used to make decisions about your health care. However, if the researchers decide that a result is important for your health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.
You may decide that you do not want your leftover samples stored for future research. You can still be in this study even if you make this decision. You may also withdraw your consent for storage and future use of your samples at any time. If you withdraw your consent, the leftover samples will be destroyed.

Please read the following statements carefully and then mark your initials in the appropriate space provided.

I allow my leftover blood samples to be stored for use in future IMPAACT-approved, HIV-related research studies.

__________ Yes __________ No __________ Date

I allow my leftover blood to be used for genetic testing as part of future IMPAACT-approved, HIV-related research studies.

__________ Yes __________ No __________ Date

**HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**
About 450 mothers and babies have already taken part in this study. Another 450, for a total of about 900, are expected to take part.

**HOW LONG WILL I BE IN THIS STUDY?**
The amount of time you will be in this study depends on whether your baby is infected with HIV. If your baby is not infected with HIV, you will have one study visit. If your baby is infected with HIV, you will be in the study for as long as your baby, up to 9 years.

**WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?**
The study doctor may need to take you off the study early without your permission for the reasons listed below. If this happens, no further information will be collected, and no further study visits or laboratory tests will be done.

- You and/or your baby do not have HIV infection.
- Your baby meets conditions to leave the study.
- You stop coming to the clinic for study visits.
- The study doctor determines that further participation would be harmful to your health or well-being.
- The study is stopped or cancelled.

**WHAT ARE THE RISKS OF THE STUDY?**
Blood drawing may cause some discomfort, bleeding, or bruising where the needle enters the body. A small blood clot may form at the site where the blood was drawn or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur.

**ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?**
This study may be of no direct benefit to you or your baby. Information learned from this study may help others who have HIV. If your baby is infected with HIV, this study may help control the amount of HIV in your baby’s body.
WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?
You may choose to not take part in this study. You may leave the study at any time. Please talk to the study staff about other choices available to you. This study does not provide HIV-related care and treatment for mothers. Whether or not you choose to take part in the study, the study staff will tell you about other sources of HIV-related care available to you and your baby.

WHAT HAPPENS IF I AM INJURED?
If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form. [Note to sites: This paragraph may be modified to reflect your institutional policies and procedures, but the statement regarding compensation through the NIH should not be changed.]

WHAT ABOUT CONFIDENTIALITY?
US sites
Efforts will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the US Food and Drug Administration.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

Your study records may be reviewed by:
- [insert name of site IRB/EC]
- [insert name of site drug regulatory entity]
- [insert name of other site regulatory entities]
- The US National Institutes of Health and its study monitors
- The US Food and Drug Administration
- The US Office for Human Research Protections
- Other US, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The company that makes one of the ARVs given to babies in this study (Merck Research Laboratories)

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This web site will not include information that can identify you. At most, the web site will include a summary of the study results. You can search this web site at any time.
Sites outside the US:
Efforts will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your study records may be reviewed by:
- [insert name of site IRB/EC]
- [insert name of site drug regulatory entity]
- [insert name of other site regulatory entities]
- The US National Institutes of Health and its study monitors
- The US Food and Drug Administration
- The US Office for Human Research Protections
- Other US, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The company that makes one of the ARVs given to babies in this study (Merck Research Laboratories)

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This web site will not include information that can identify you. At most, the web site will include a summary of the study results. You can search this web site at any time.

WHAT ARE THE COSTS TO ME?
There is no cost to you for your study visits or blood tests.

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study. [Note to sites: Language related to insurance can be deleted if it is not relevant to your site.]

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?
Taking part in this study is completely voluntary. You may choose to not take part in this study. However, if you choose to not take part, your baby cannot take part. If you choose to take part, you may leave this study at any time. If you leave the study, your baby can stay in the study, if you agree to that. Your decisions will not have any impact on your participation in other studies conducted by the National Institutes of Health and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want to learn the results of this study when they are available, please let the study staff know.
WHAT SHOULD I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
  • name of the investigator or other study staff
  • telephone number of above

For questions about your rights as a research participant, contact:
  • name or title of person on the IRB/EC or other organization appropriate for the site
  • telephone number of above

SIGNATURES

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to take part in this study, please sign your name below.

Participant’s Name (print)  Participant Signature  Date

Study Staff Conducting Consent Process Name (print)  Study Staff Signature  Date

Witness Name  Witness Signature  Date